Update: Viral Hepatitis A-E but not (yet) the LMNOPs

SC DHEC Immunization Conference
Fri. November 7, 2008

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SC DHEC Regions 6 & 7
with thanks to Leigh Beasley, MD FAAFP, the CDC, and others for several slides

Case Study: ? Viral hepatitis

- A 35 yo M presents with a 5 day Hx of malaise, anorexia, nausea, mild upper abdominal discomfort
- PMHx reveals no unusual risk factors, travel, etc.
- His companion is aSx.
- Exam is unremarkable except for questionable icterus
- He agrees to some lab tests but has no insurance
- Q: what tests do you order to maximize chance of specific Dx while holding charges down? (remember: not all "hepatitis panels" are created equal)

Case Study: ? Viral hepatitis

- Q: what tests do you order to maximize chance of specific Dx while holding charges down?
- CBC, sed rate, basic LFTs (ie, ALT, AST, GGT)
- HAV-Ab-IgM
- HBsAg, HBcAb-IgM
- HCV Ab
- HEV Ab
- ? Other serologies (ie, ehrlichiosis) if indicated

Viral Hepatitides A-E

www.cdc.gov/hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ specific body fluids	blood/ specific body fluids	blood/ specific body fluids	feces
Route of transmission	fecal-oral orogenital	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral orogenital
Asymptomatic infection	~1/3	~1/2	~2/3	~9/10	~1/5
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure Immunization, IG	pre/post-exposure immunization, blood donor screening, IG, etc	blood donor screening, IDU cessation, safer sex	pre/post-exposure immunization	ensure safe drinking water

All are preventable via personal risk behavior modification

R. Ball, MD, MP

Acute Viral Hepatitis: symptoms?

VIRUS	Symptoms up to	aSx up to
HAV	~2/3	~1/3
HBV	~1/2	~1/2
HCV	~1/3	~2/3

Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, USA

	HAV	HBV	HCV	HDV	HEV
Acute infections (x 1000)/year*	125-200	140-320	35-180	6-13	?
Fulminant deaths/year	100	150	?	35	
Chronic infections	0	1-1.25 million	**~ 4-6 million**	70,000	
Chronic liver disease deaths/year	0	5,000	8-10,000	1,000	

* Range based on estimated annual incidence, 1984-1994.

HIV estimate ~ 1+ million

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

R. Ball, MD, MPH

Starts on page 26

In U.S., significant reduction in acute hepatitis rates

Rates of acute hepatitis in the United States have reached a new low. According to the CDC, the incidence rate of hepatitis A has declined 88% since 1995; the incidence rate of hepatitis B has declined 79% since 1990. These incidence rates are the lowest ever reported.

The CDC also reported that among children, the most significant reductions were in states that required routine childhood vaccination against hepatitis.

Despite the benefits of vaccination on reducing rates of hepatitis A and hepatitis B in the United States, hepatitis C affects approximately 3.2 million Americans. Because no vaccine is available, recommendations against hepatitis C focus on prevention efforts to decrease risk for transmission.

For more on hepatitis rates, see page 29.

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Surveillance Summaries March 21, 2008 / Vol. 57 / No. SS-2

Surveillance for Acute Viral Hepatitis — United States, 2006

Viral Hepatitis Cases in SC: 1-6/2007

TYPE	ACUTE	CHRONIC	vs. 1-6/06
HAV	5	n/a	11
HBV	5	306	385
HCV	no test	**2573**	**2775**
HDV	?	?	1
HEV	1	n/a	1

Reporting required by attending physician/designee and laboratory except where lab only (L) reporting is indicated.

Report IMMEDIATELY By Phone

- ☣ Any outbreak or unusual disease or cluster of cases
- ☣ Any potential biological (to include toxins such as ricin), chemical, or terrorist event (1)
- Animal (mammal) bites
- ☣ Anthrax (7)
- ☣ Botulism
- ☣ Foodborne outbreak - unusual cluster
- *Haemophilus influenzae* type b, invasive disease (4) (7)
- Influenza A - Avian or Novel (Not H1 or H3)
- Measles (Rubeola)
- Meningococcal disease (4) (7) (9)
- ☣ Plague (7)
- Poliomyelitis, Paralytic and Nonparalytic
- SARS, Severe Acute Respiratory Syndrome
- ☣ Smallpox
- ☣ Viral Hemorrhagic Fever

Urgently Reportable Within 24 Hours By Phone

- Arboviral Neuroinvasive Disease (acute infection, including acute flaccid paralysis, atypical Guillain- Barré Syndrome): Eastern Equine Encephalitis (EEE), LaCrosse (LAC), St. Louis Encephalitis (SLE), West Nile Virus (WNV) (7)
- ☣ Brucellosis (7)
- Dengue
- Diphtheria (7)
- E-coli, shiga toxin-producing (STEC), including O157:H7 (7)
- ☣ Glanders *(Burkholderia mallei)* (7)
- Hantavirus
- Hemolytic uremic syndrome (HUS)
- Hepatitis A, acute (IgM Ab+ only)
- Hepatitis B, acute (HBcAb-IgM +)
- ☣ Melioidosis *(Burkholderia pseudomallei)* (7)
- Mumps
- Pertussis
- ☣ Q fever *(Coxiella burnetti)*
- Rabies (human)
- Rubella (includes congenital)
- *Staphylococcus aureus*, vancomycin-resistant (VRSA/VISA) (7)
- Syphilis, primary or secondary (lesion or rash)
- Syphilis, congenital
- Trichinosis
- Tuberculosis (7)
- ☣ Tularemia
- Typhoid fever *(Salmonella typhi)* (7)
- ☣ Typhus fever, epidemic *(Richettsia prowazekii)*
- Vibrio infections - all types, including *Vibrio cholerae* O1 and O139
- Yellow Fever

Report Within 7 Days

- AIDS (2)
- Campylobacteriosis
- Chancroid
- Chlamydia trachomatis, genital site (L)
- Creutzfeldt-Jakob Disease (Age < 55 years)
- Cryptosporidiosis
- Cyclosporiasis
- Ehrlichiosis
- Giardiasis
- Gonorrhea
- *Haemophilus influenzae*, non-type b invasive disease (4)(7)
- Hepatitis B, chronic
- Hepatitis B Surface Antigen+ (HBsAg+) with each pregnancy
- Hepatitis C, D, E
- HIV-1 or HIV-2 infection (2)
- HIV CD4 co receptor (L)
- HIV CD4 T-lymphocyte count/percentage - all results (L) (2)
- HIV viral load - all results (L) (2)
- HIV HLA-B5701 (L)
- HIV subtype, genotype, and phenotype (L)
- Influenza, positive rapid flu test (report # of positive results)
- Influenza, positive virus culture isolates (L)
- Influenza, pediatric deaths - age ≤ 17 years
- Lead poisoning (5)
- Lead tests, all (6) (L, includes office tests)
- Legionellosis
- Leprosy (Hansen's Disease)
- Leptospirosis
- Listeriosis (7)
- Lyme disease
- Lymphogranuloma venereum
- Malaria
- Meningitis, aseptic (8)
- Pesticide poisoning
- ☣ Psittacosis
- Rocky Mountain Spotted Fever (RMSF)
- Salmonellosis (7)
- Shigellosis (7)
- *Staphylococcus aureus* - Methicillin Resistant (MRSA) Bloodstream infections (L)
- Streptococcus group A, invasive disease (4)
- Streptococcus group B, age < 90 days
- *Streptococcus pneumoniae*, invasive, (4) (include antibiotic resistance patterns) (3)
- Syphilis, latent or tertiary
- Syphilis, positive serologic test
- Tetanus
- Toxic Shock (specify staphylococcal or streptococcal)
- Varicella
- Varicella death
- Yersiniosis

☣ Potential agent of Bioterrorism (L) Only labs are required to report. For notes 1-10, see complete list of reportable diseases at: www.scdhec.gov/health/disease/docs/reportable_conditions.pdf.

2008 SOUTH CAROLINA DEPARTMENT OF HEALTH AND ENVIRONMENTAL CONTROL DISEASE REPORTING CARD

Disease reporting is required by SC Code of Laws Section 44-29-10, Regulation 61-20, 44-1-110, and 44-1-140. **See other side for list of reportable diseases.**

Federal HIPAA legislation allows disclosure of protected health information, without consent of the individual, to public health authorities for the purpose of preventing or controlling disease. (45 CFR §164.512)

Patient Name (Last / First / Middle)

Date of Birth (Month / Day /Year)

Patient Phone Numbers

Race ☐ Asian ☐ Black ☐ White ☐ Am Ind ☐ Pac Isl ☐ Unk

Ethnicity ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Sex ☐ Male ☐ Female ☐ Not Stated

Patient Address / City / ZIP Code

County

Patient ID or SSN

If Female, Pregnant ☐ Yes ☐ No

Disease (Include stage, if appropriate)

Date of Diagnosis

Symptoms **Date of Symptom Onset:** _____

If Lyme or RMSF, Rash? ☐ Yes ☐ No

For STD Reporting Treated: ☐ Yes ☐ No Treatment Date: _____ Rx: _____

Patient Status ☐ In Childcare ☐ Food Handler

Laboratory Results

Test Date	Specimen Site

Hepatitis Jaundice ☐ Yes ☐ No AST: _____ ALT: _____ Date: _____

Hepatitis A Results Hepatitis A antibody (Acute IgM anti-HAV) ☐ Pos ☐ Neg ☐ Unk

Hepatitis C Results
Hepatitis C – EIA ☐ Pos ☐ Neg ☐ Unk s/co ratio: _____
Hepatitis C – RIBA ☐ Pos ☐ Neg ☐ Unk
Hepatitis C – PCR ☐ Pos ☐ Neg ☐ Unk
Hepatitis C – Viral Load _____

Hepatitis B Results

	Pos	Neg	Unk
Hepatitis B surface Antigen (HBsAg)	☐	☐	☐
Hepatitis B core Antibody IgM (HBcAb-IgM)	☐	☐	☐
Hepatitis B core Antibody Total (HBcAb)	☐	☐	☐
Hepatitis B surface Antibody (HBsAb)	☐	☐	☐
Hepatitis B e Antigen (HBeAg)	☐	☐	☐

Responsible Physician & Phone #

Reporting Lab/Facility, Person, & Phone #

Date Reported to Health Dept.

☐ **Send More Cards To: (Address)**

Mail or Call Reports To:
DHEC Region 7 - Charleston
4050 Bridge View Drive, Suite 600
N. Charleston, SC 29405 Attn: Epi Nurse
Phone: (843) 746-3860 or 746-3800
Fax: (843) 746-3851
Nights/Weekends: (843) 219-8470

For daytime & after-hours phone numbers: www.scdhec.gov/health/disease/docs/reportable_conditions.pdf
For after-hours reporting of immediately reportable conditions, call state answering service: 1-888-847-0902
For more information, call the DHEC Bureau of Disease Control in Columbia: 803-898-0861 (M-F 9-5)

DHEC 1129 (01/2008) DHEC Use Only: County Review Date State Review Date C P S N

H E C

PROMOTE PROTECT PROSPER

Hepatitis A – Clinical Features

- **Incubation period:** **Average 30 days**
  Range 15-50 days
- **Jaundice by age group:**
  - **< 6 yrs** <10%
  - **6 – 14 yrs** 40%-50%
  - **> 14 yrs** 70%-80%
- **Rare Complications:** Fulminant hepatitis (death 1-2%)
  Cholestatic hepatitis
  Relapsing hepatitis
- **Chronic sequelae:** None
- **Treatment:** Supportive

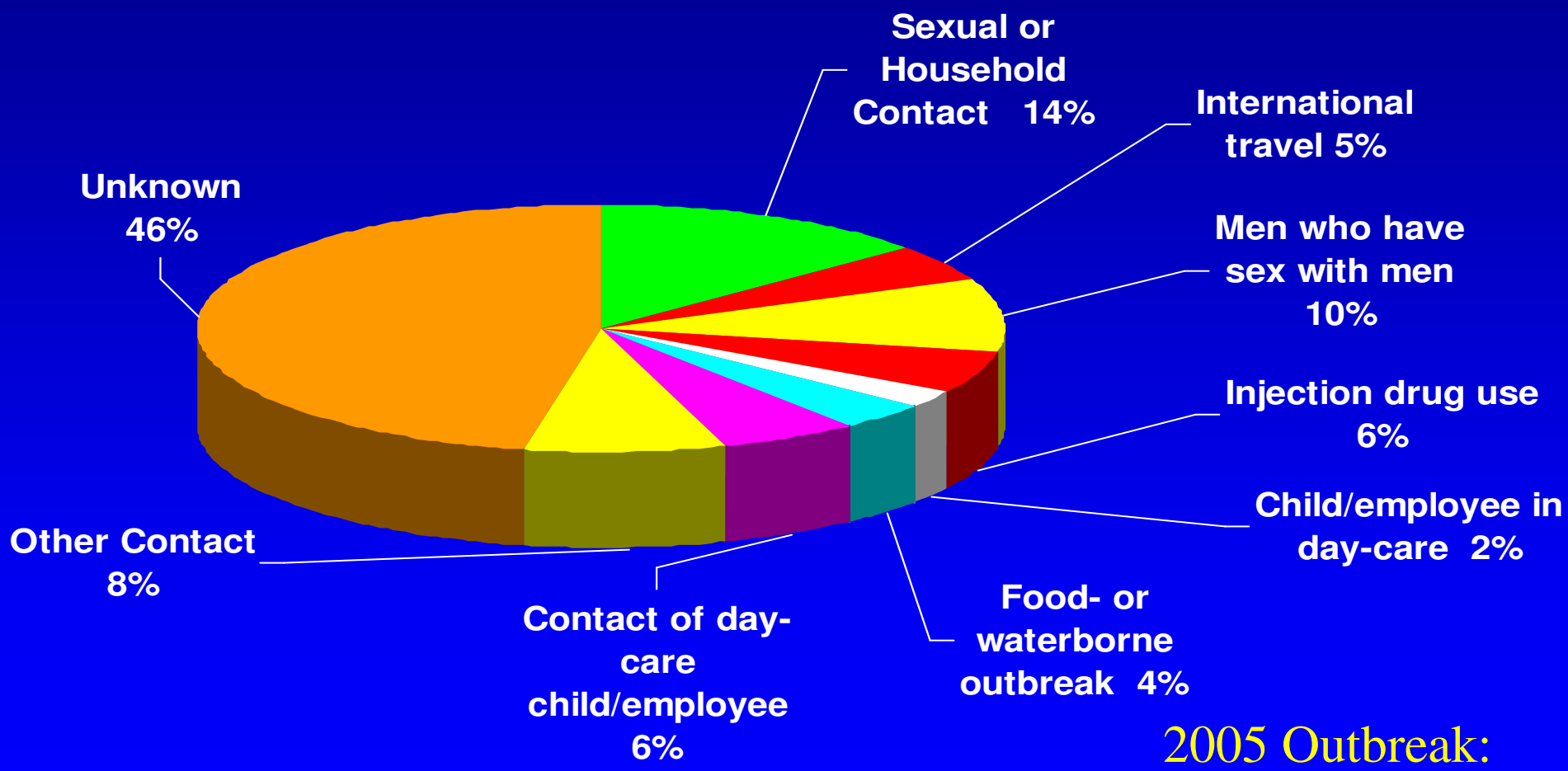
Case Study: Viral Hepatitis A

- A 55 yo WF presents with malaise, anorexia, weight loss, nausea, and vague abdominal pain.
- Her exam shows a moderately ill WF INAD but with mild upper abd. tenderness and ? mild icterus
- Her LFTs show ↑ Alk.Phos, Bili, AST (SGOT), with ↓ T.Prot., Albumin, and normal ALT (SGPT).s
- Her viral hepatitis serologies are (-) except for (+) HAV-Ab-IgM.
- What is your Dx, workup, Rx & Mx?

Case Study: Viral Hepatitis A

- A 55 yo WF w/ Sx & Sg of acute viral hepatitis, with ↑ LFTs & (+) HAV-Ab-IgM.
- What is your Dx, workup, Rx & Mx? …..
- Day 13: Husband was given IG as HAV PEP, but then his HAV-Ab-total returned (+), with IgM (-) = old infection.
- Repeat serologies: HAV-Ab-IgM AND total Ab both (-)
- Abd CT scan: intrahepatic masses. CEA ↑ 1342 (nl <2.5)
- Liver Bx: undifferentiated CA. ChemoTx decision pending
- Lab testing: no direct data to support a false (+) IgM Ab…

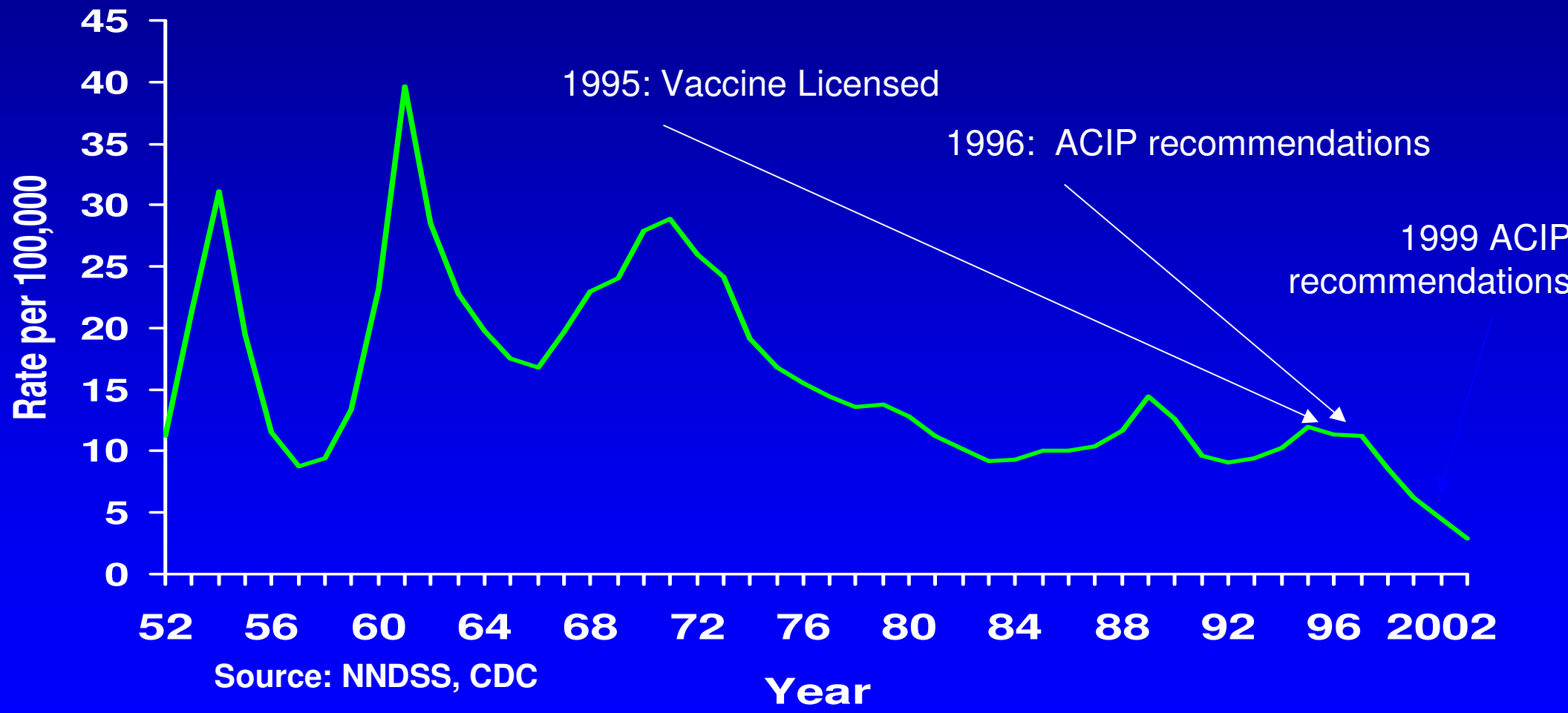
Hepatitis A: Risk Factors 1990-2000, USA



2005 Outbreak: green onions

Source: CDC: NNDSS/VHSP

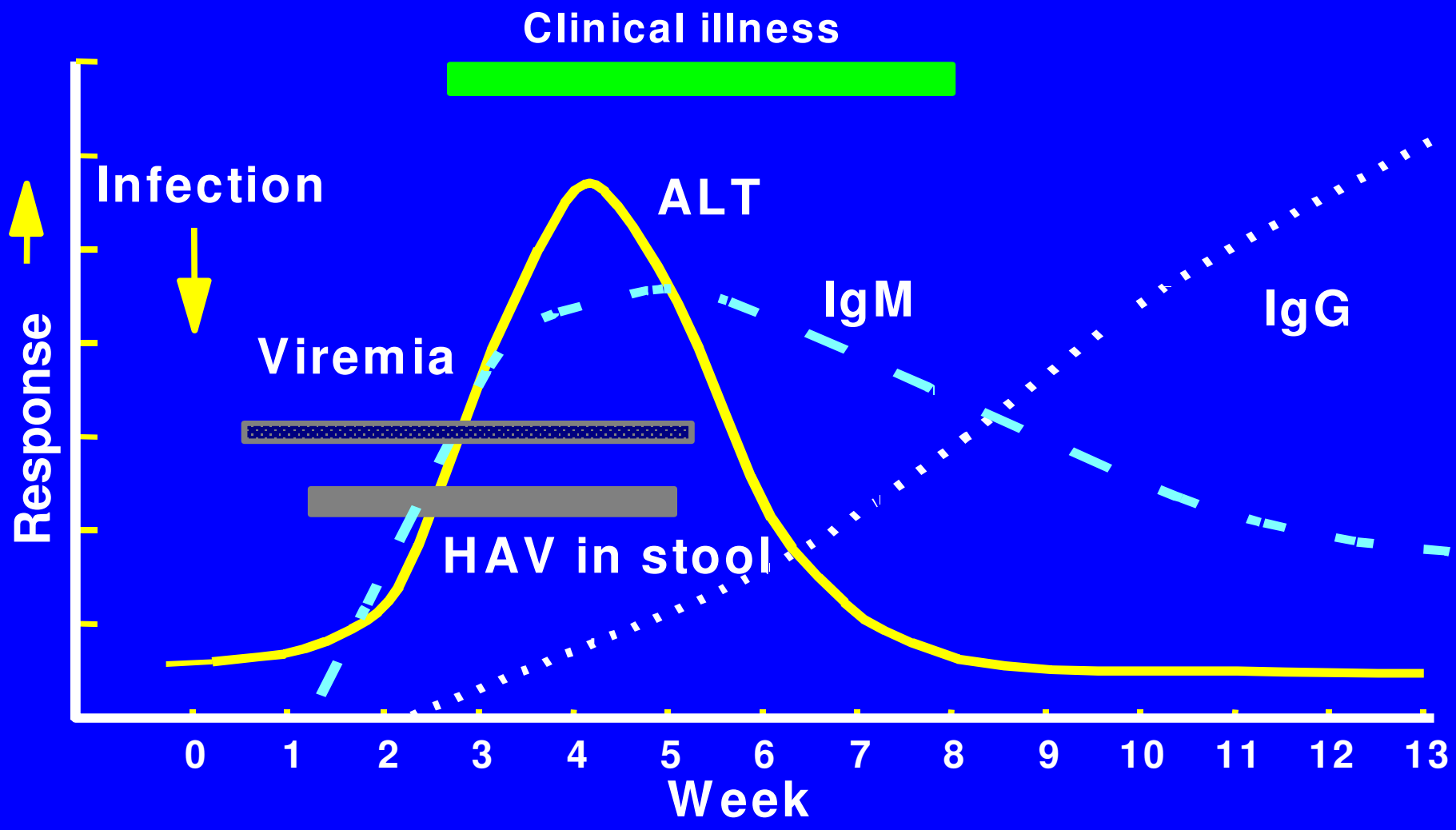
Reported Cases of Hepatitis A, United States



Source: NNDSS, CDC

Vaccine highly effective (single strain RNA picornavirus)

EVENTS IN HEPATITIS A VIRUS INFECTION



Hepatitis A Case Determination

HAV-Ab-IgM (usually clears in ~4-6 mos.)	**HAV-Ab-IgG (or total Ab)**	**Interpretation**
Positive	**Positive**	**Confirmed – Acute Case**
Positive	**Unknown**	**Confirmed – Acute Case**
Negative/ Unknown	**Positive**	Past Infection – Not Reportable to Public Health

Acute Hepatitis ? Etiology: order HAV-Ab-IgM, not total Ab

(+) Antibody (Ab)	LFTs	Clinical status
• **TOTAL (IgG & IgM)**	↑ or ?	= Unknown = prob. old resolved hepatitis A.
• **IgM (HAV Ab-IgM)**	↑ or ?	= ACUTE Hep A Hence, the (+) IgM Ab defines the acute stage and usually clears after ~ 4-6 months.

- **Intervention**: HAV vaccine and/or IG for household, other close contacts within 2 weeks of last contact, otherwise heightened awareness and perhaps serologic testing in 2 months if aSx & concerned. DHEC/ public health may occas. contact restaurant patrons (unusual to do so in SC).

HEPATITIS A INFECTIVITY/ PEP TIMELINE

2 week window of opportunity for IG PEP

Focus on: Period of Infectivity of hepatitis A virus (HAV) in stool of person with acute hepatitis A, for consideration of Immune Globulin (IG) Post-Exposure Prophylaxis (PEP):

Diagnosis occurs →

Exposure		**Incubation Period**		**Infection →**				
(-) 4 weeks	**(-) 3 wks**	**(-) 2 wks**	**(-) 1 wk**	**DAY 0**	**(+) 1 wk**	**(+) 2 wks**	**(+) 3 wks**	**(+) 4 wks**
				Symptom onset (Sx in 2/3, usually nonspecific; jaundice occurs on ? day, if it occurs at all, whether detected clinically or chemically…)				
IgM:	**(-)**	**(-)**	**(-)**	**(+)**	**(+)**	**(+)**	**(+)**	**(+)**

HAV in stool (∴ communicable to others via fecal-oral route + poor handwashing) = PERIOD OF INFECTIVITY:

(-)	**(-)**	**(+)**	**(+)**	**(+)**	**(+)**	**(+?)**	**(-)**	**(-)**

Bona fide contacts (ie, household, close personal, day care center, uncooked handled-food recipients, etc) are eligible for IG Post-Exposure Prophylaxis (PEP) if their LAST day of bona fide contact was during the **PERIOD OF INFECTIVITY** of the index patient AND ALSO ≤ 14 days from the day of discussion and contemplated IG PEP.

Robert Ball, MD, MPH draft #1, 11/03

HAV Prevention: Vaccination & Immune Globulin

- **Pre-exposure (vaccine and/or IG)**
  - travelers to intermediate and high HAV-endemic regions
  - Individual risk setting
- **Post-exposure: vaccine or IG (within 14 days)**

Routine

  - household and other intimate contacts

Selected situations

  - institutions (e.g., day care centers)
  - common source exposure (e.g., food prepared by infected food handler)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 25, 2007 VOL. 357 NO. 17

Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

John C. Victor, Ph.D., M.P.H., Arnold S. Monto, M.D., Tatiyana Y. Surdina, M.D., Saida Z. Suleimenova, M.D., Gilberto Vaughan, Ph.D., Omana V. Nainan, Ph.D.,* Michael O. Favorov, M.D., Ph.D., Harold S. Margolis, M.D., and Beth P. Bell, M.D., M.P.H.

CONCLUSIONS

Low rates of hepatitis A in both groups indicate that hepatitis A vaccine and immune globulin provided good protection after exposure. Although the study's prespecified criterion for noninferiority was met, the slightly higher rates of hepatitis A among vaccine recipients may indicate a true modest difference in efficacy and might be clinically meaningful in some settings. Vaccine has other advantages, including long-term protection, and it may be a reasonable alternative to immune globulin for post-exposure prophylaxis in many situations. (ClinicalTrials.gov number, NCT00139139.)

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Weekly
October 19, 2007 / Vol. 56 / No. 41

BOX. Summary of updated recommendations for prevention of hepatitis A after exposure to hepatitis A virus (HAV) and in departing international travelers

Postexposure prophylaxis

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible.

- For healthy persons aged 12 months–40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred.
- For persons aged >40 years, IG is preferred; vaccine can be used if IG cannot be obtained.
- For children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.

Update: Prevention of Hepatitis A After Exposure to Hepatitis A Virus and in International Travelers. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)

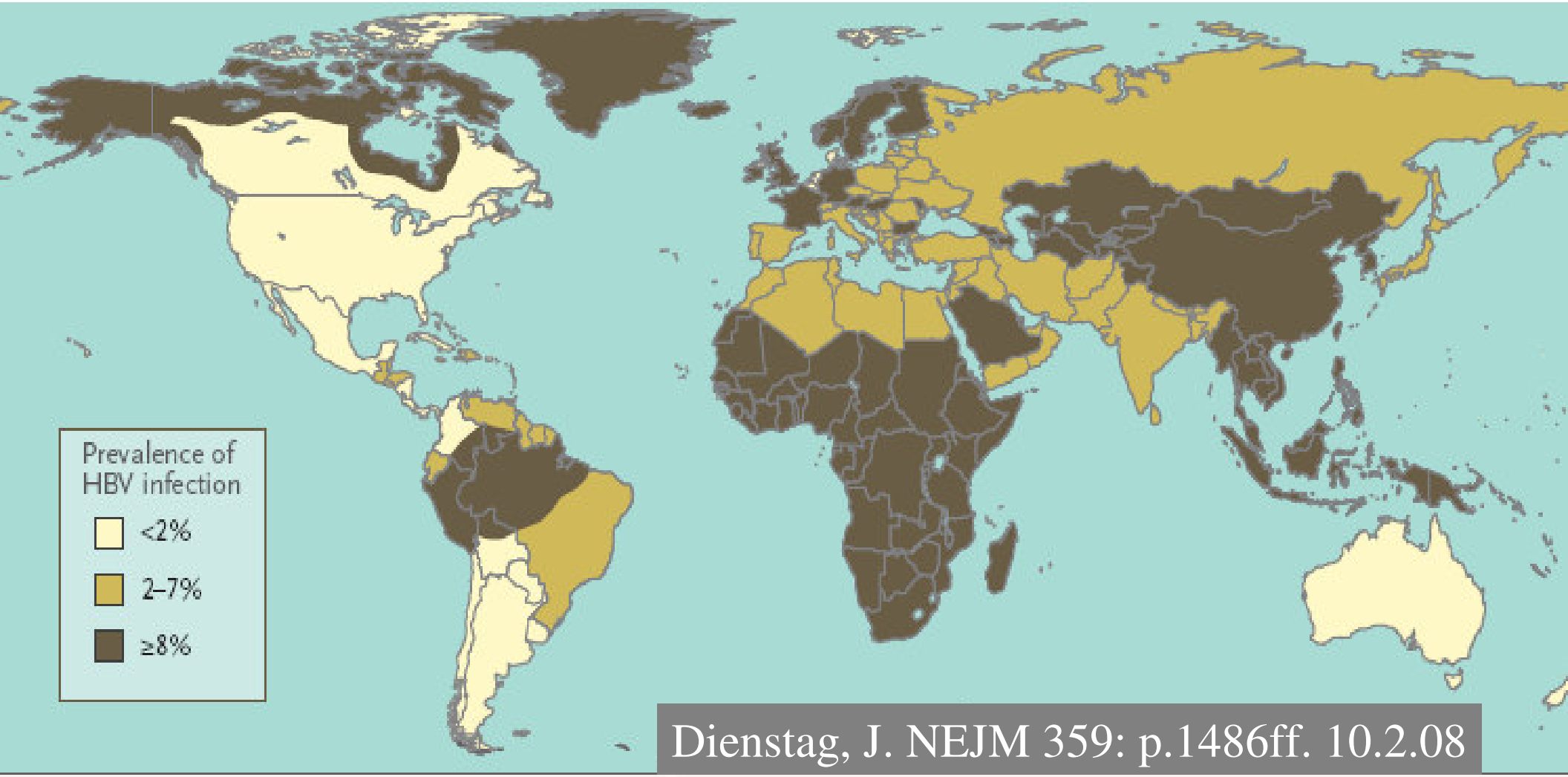
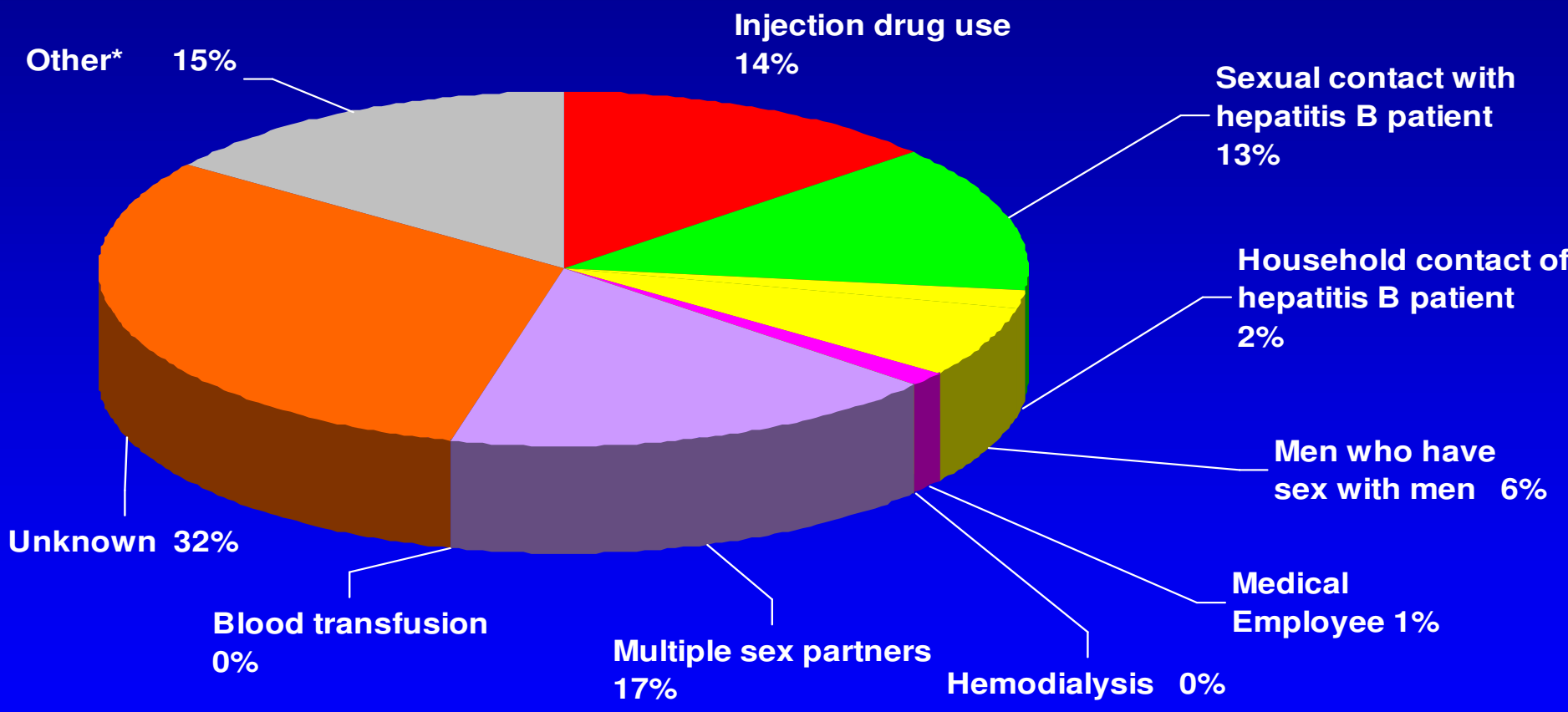


Figure 2. Clinical and Epidemiologic Correlations in HBV Infection.

The clinical expression of HBV infection depends on the time of life when the infection is acquired. In Asian countries with a high preva ence of HBV infection, HBV is acquired perinatally from infected mothers. It is not accompanied by acute hepatitis, but it results in chronic infection in more than 90% of patients. Later in life, cirrhosis and hepatocellular carcinoma account for up to a 40% lifetime ris of death. In contrast, in Western countries with a low prevalence of HBV infection, HBV is rarely acquired perinatally but instead is ac- quired during adolescence and early adulthood; infections acquired in adulthood usually cause a clinically apparent acute hepatitis, but progression to chronic hepatitis is rare, as is the risk of hepatocellular carcinoma.

Risk Factors Associated with Reported Hepatitis B, 1990-2000, United States



*Other: Surgery, dental surgery, acupuncture, tattoo, other percutaneous injury

Source:

Case Study: Viral Hepatitis B

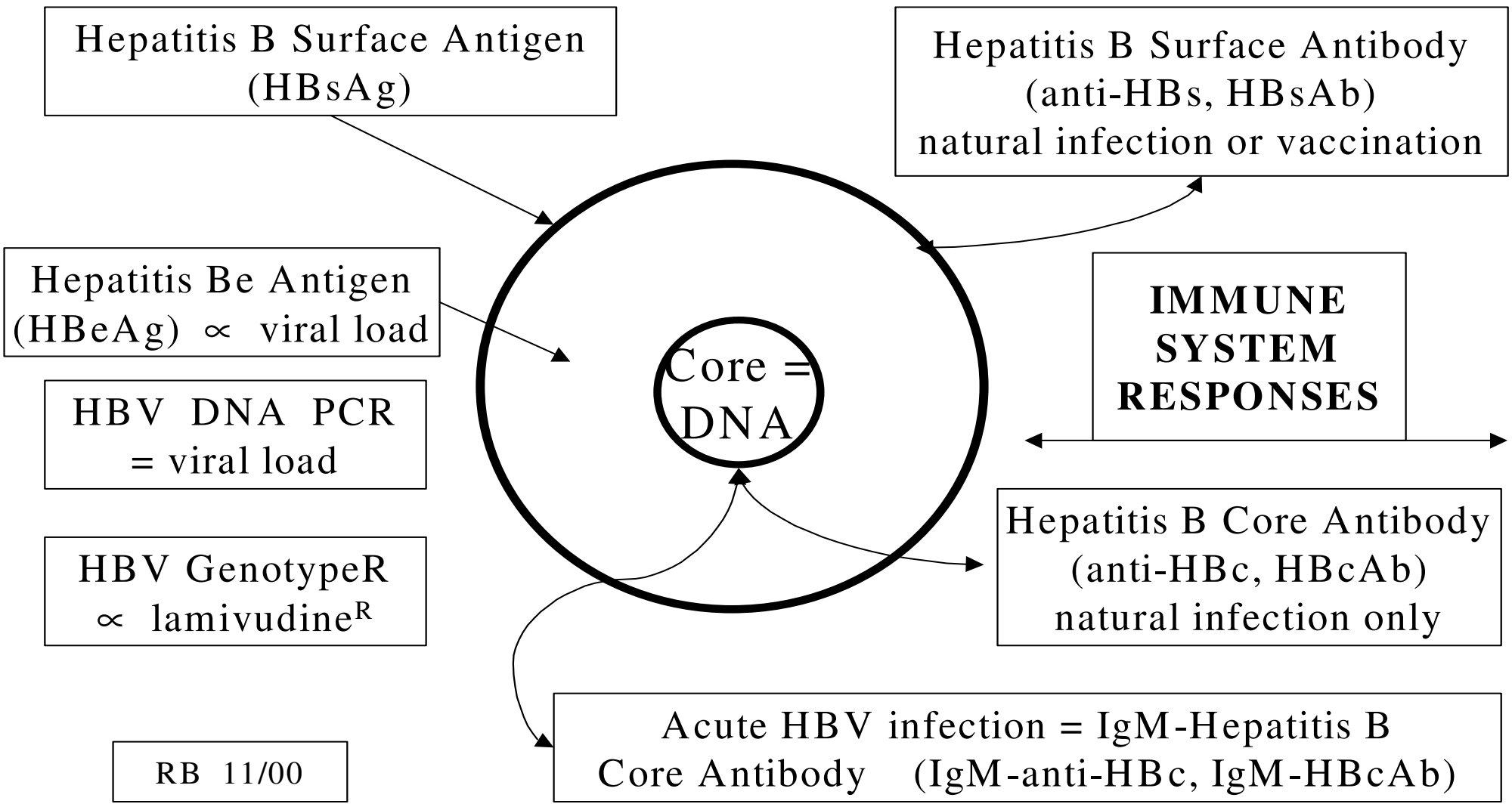
- A 52 yo BF presents with recent malaise, anorexia, nausea, vague abdominal pain, dyspnea.
- PMHx: DM, RA.
- Her exam shows a moderately ill BF INAD but with mild upper abd. tenderness. CXR: c/w sarcoidosis, pulm HTN.
- Her LFTs show ↑↑ Alk.Phos, GGT, but ~↑ AST & ALT. ↓↓ T.Prot., Albumin, H/H.
- Viral hepatitis serologies: (+) HBcAb-IgM, (-) HBsAb; (-) HCV Ab.
- What is your Dx, workup, Rx & Mx?

Case Study: Viral Hepatitis B

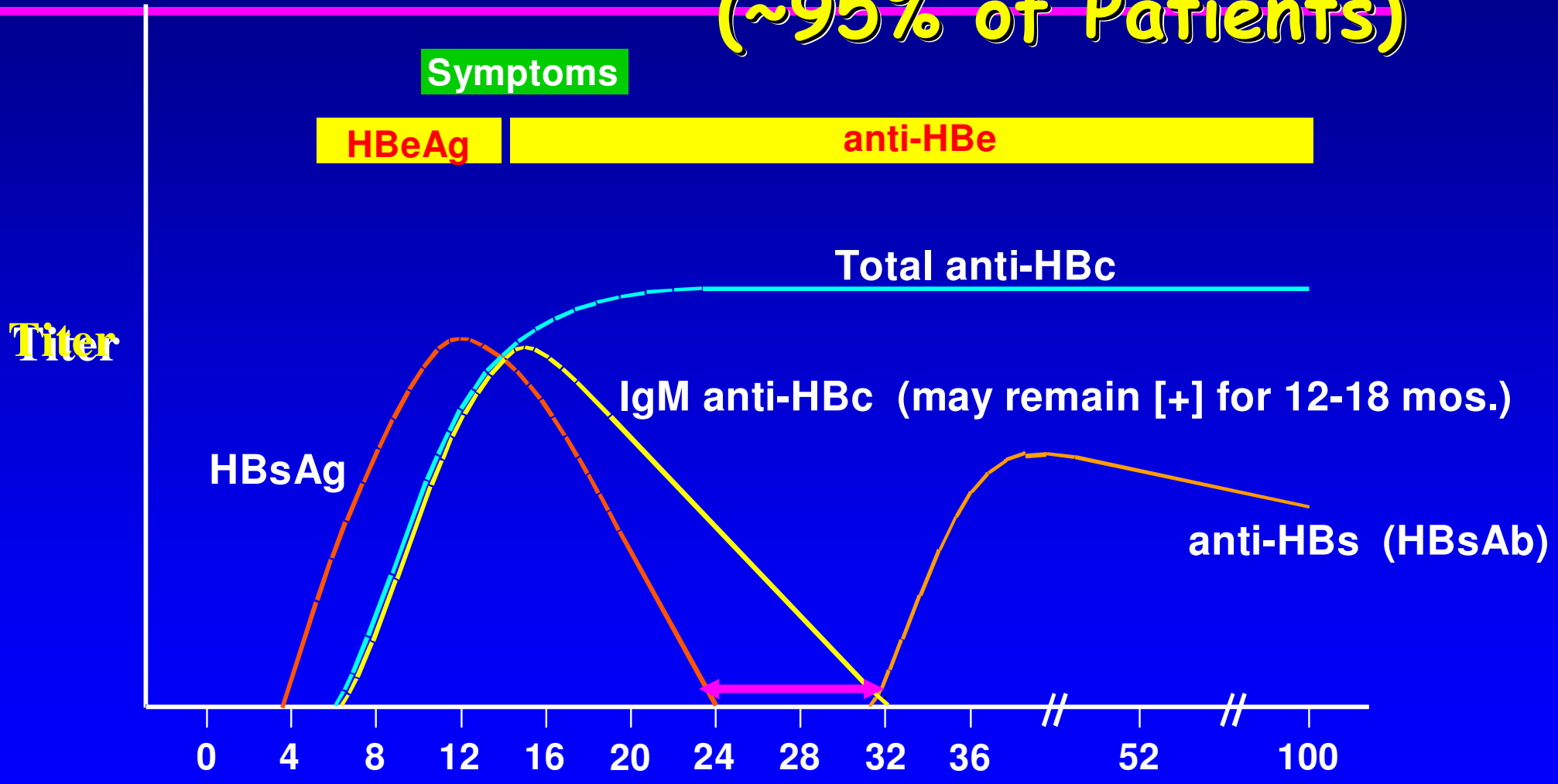
- A 52 yo BF w DM, RA, sarcoidosis, pulm. HTN, & now Sx & Sg of acute viral hepatitis, with ↑ LFTs & (+) HBc-Ab-IgM.
- Does she really have acute HBV also? Is this a case?

- Husband was offered free HBV testing (at health dep't, & free HBV vaccination if indicated), but he declined…
- Repeat patient serologies STRONGLY recommended by DHEC I.D. epidemiologist to attending physician, but…

HEPATITIS B VIRUS : Structure & Function

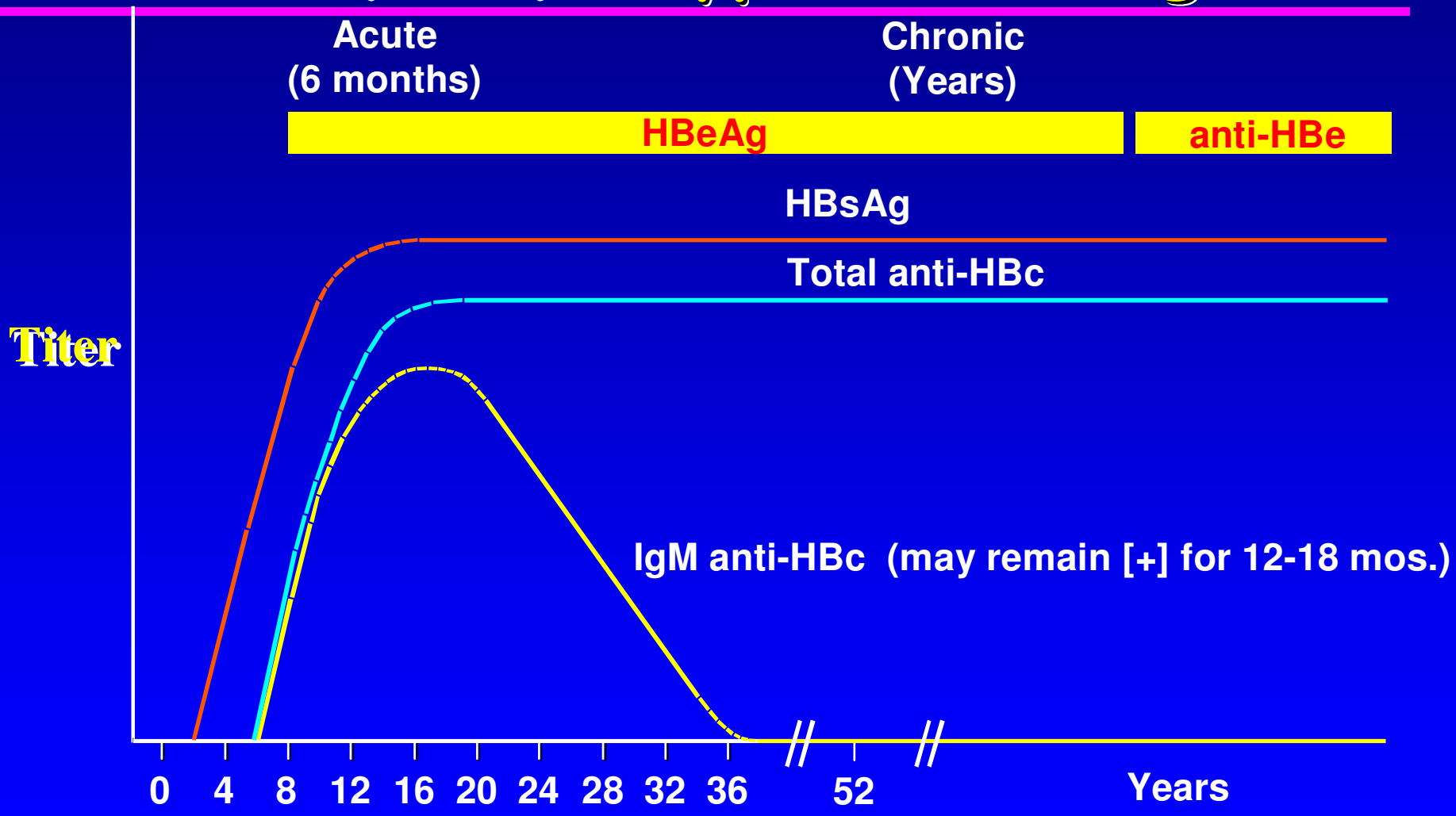


Acute Hepatitis B Virus Infection w Recovery- Typical Serologic Course (~95% of Patients)



R. Ball, MD, MPH

Progression to Chronic Hepatitis B Virus Infection (~5%)- Typical Serologic Course



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Hepatitis B – Serologic Markers

	HBsAg	HBsAb	HBcAb	HBcAb-IgM
Late Incubation Period	+	-	-	+/-
Acute Infection	+	-	+	+
Chronic Infection	+	-	+	-
Recent Infection (≤ 6-12 Months)	-	+/-	+	+
Resolved Infection (>12 months)	-	+	+	-
Immunized	-	(+) always = IMMUNE	-	-

HEPATITIS B SEROLOGIES

www.cdc.gov/hepatitis

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

HBV Serologic idiosyncrasies- 1

HBcAb-IgM: does a (+) result always mean "acute infection"?

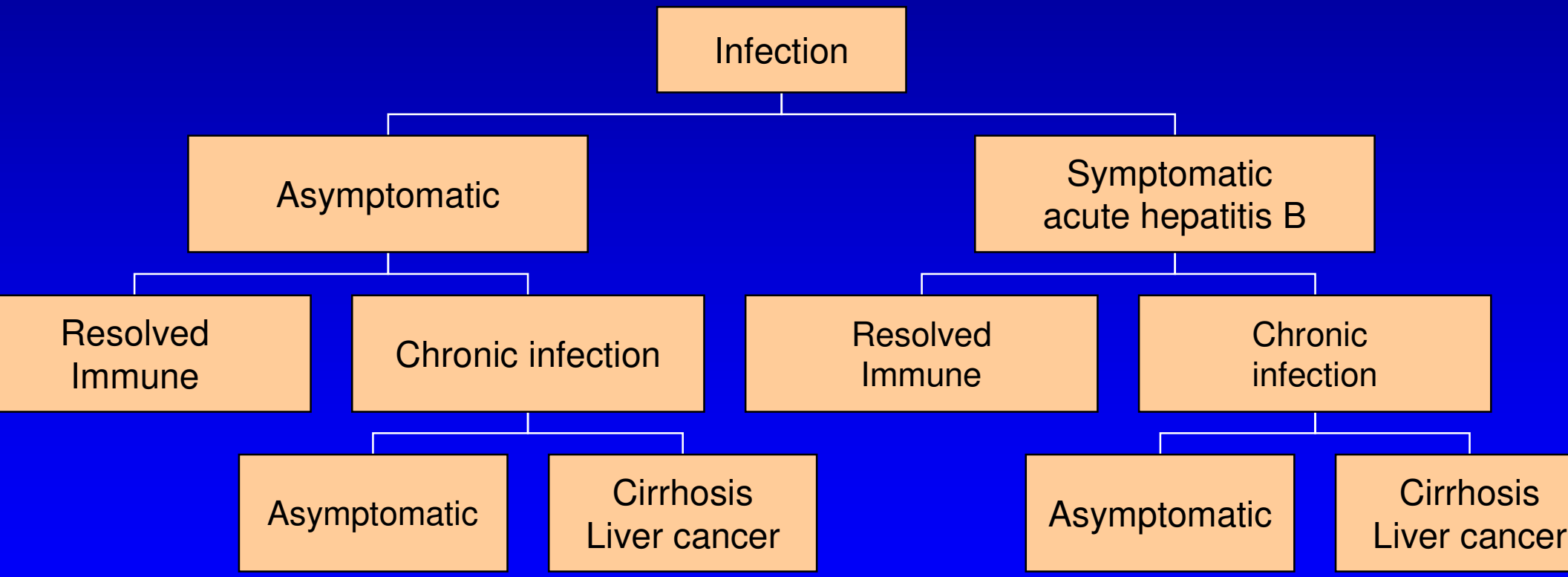
- IgM follows acute infection, so by definition a true (+) defines "acute" for surveillance purposes- [confirm w/ repeat testing if you question 1st result]
- HBcAb-IgM may persist for up to 2 years in up to 20% of patients with acute HBV infection, slowly resolving during this time [rare false (+)s occur]

HBV Serologic idiosyncrasies- 2

Concurrent (+) HBsAg and HBsAb: a rare event, but how does it occur?

- Usually: slowly resolving HBsAg with rapid production of protective HBsAb ("overlap")
- Chronic HBV: intermittent virus reactivation w/ "booster effect", Δ immune complexes→ (+) HBsAb
- Rarely: Δ HBV geno-/sub-types, false (+) [lab error]

Outcomes of HBV Infection



HBV: 1^0 & 2^0 Prevention Activities

Group	Risk	Intervention
Neonates	Chronic disease	Hepatitis B vaxn.
Pre-adolescents	STD/ blood exposure	"
Adults	Occupational Exposure	" and *
		* specific PEP
Adults	STD Clinics	Hepatitis B testing, vaccinations

Post-Exposure (2^0) Testing & Prophylaxis (HBIG, vaccine):

If bona fide close/ intimate contact of HBsAg(+) case within 2 weeks of last exposure: done "free" in DHEC STD Clinics…

Immunization & Education to Eliminate HBV Transmission, United States

- Education re: Viral Hepatitis/ BBPs/ STDs
- Prevent perinatal HBV transmission (prenatal HBsAg)
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
  - all children up through age 18
- Vaccination of adults in high-risk groups
- ? Universal immunization
- Curative treatments

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | September 19, 2008 / Vol. 57 / No. RR-8

Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection

Hepatitis B Vaccine Protection

- CDC. MMWR. Immunization of HCWs. Vol. 46, # RR-18, 12/26/97 → **MMWR Vol.50, # RR-11, 6/29/01**
- "If the exposed person had an adequate Ab response (HBsAb > 10 mIU/mL) documented after vaccination, no testing or treatment is needed…" [re: exposure Mx]
- **ONCE IMMUNE (~95%), ALWAYS PROTECTED**
- **"Booster doses of HBV vaccine are not necessary, and periodic serologic testing… is not recommended."**
- **> TABLE for management of HCW exposures...**

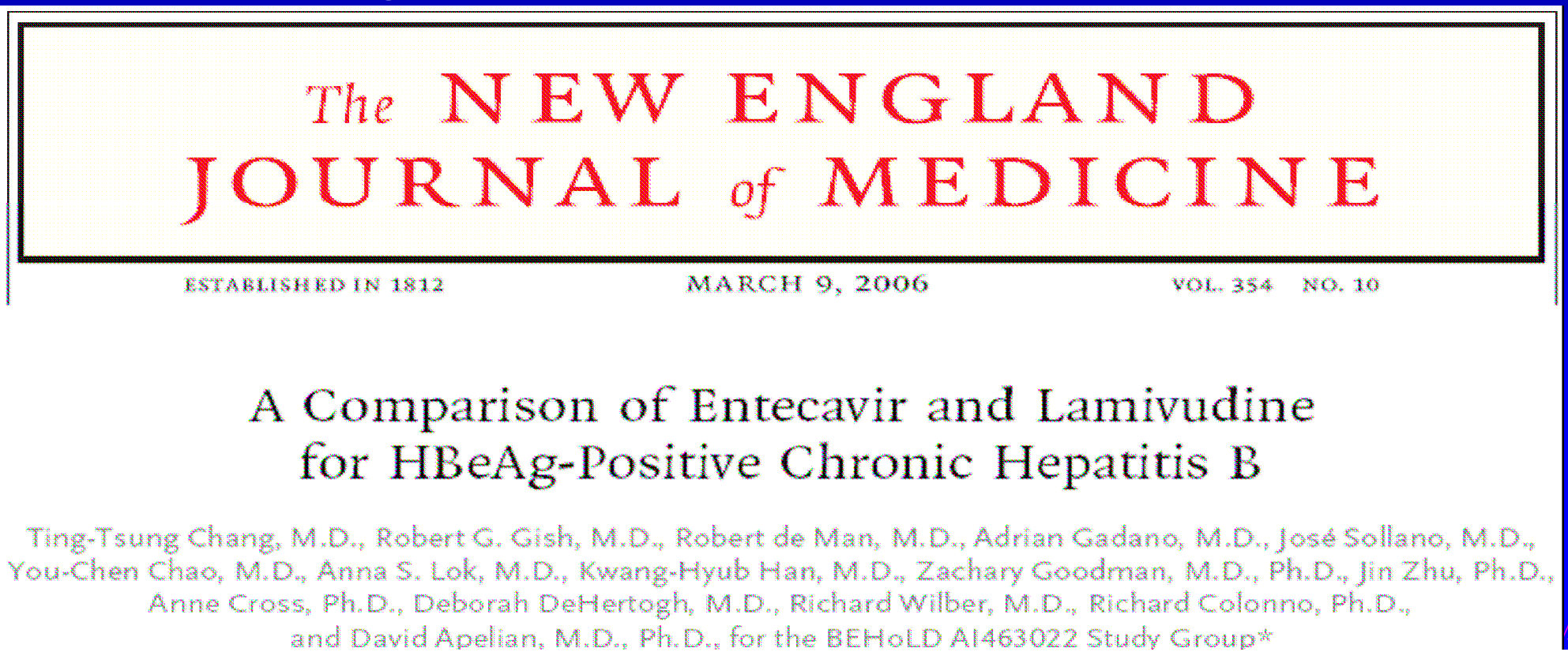
CDC BBP PEP Guidelines 2001: HCW HBV Postexposure Mx & PEP

HBV Vax'n & HBsAb status	HCP Treatment when source HBsAg(+)	(-)	unknown
Unvaccinated	HBIG x1 & *	*Start HB Vax'n	
< 1 week window for PEP decision (PDR: 2 wks)>			
Previously vaccinated			
- Known responder:	**No treatment**	**No Tx**	**No Tx**
- Known nonrespon.:	HBIG x1 & * or HBIG x2	No Tx	Tx…
- HBsAb unknown:	Test exposed for HBsAb/ if (-), Tx (HBIG x1 +booster)	No Tx	Test ...

R. Ball, MD, MPH

HBV treatment agents used in US

Interferon, peg-IFN
Adefovir (Hepsera®)
Telbivudine (Tyzeka®)
Lamivudine [3TC] (Epivir-HBV®)
Entecavir (Baraclude®)
Tenofovir (Viread)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2006 VOL. 354 NO. 10

A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B

Ting-Tsung Chang, M.D., Robert G. Gish, M.D., Robert de Man, M.D., Adrian Gadano, M.D., José Sollano, M.D., You-Chen Chao, M.D., Anna S. Lok, M.D., Kwang-Hyub Han, M.D., Zachary Goodman, M.D., Ph.D., Jin Zhu, Ph.D., Anne Cross, Ph.D., Deborah DeHertogh, M.D., Richard Wilber, M.D., Richard Colonno, Ph.D., and David Apelian, M.D., Ph.D., for the BEHoLD AI463022 Study Group*

AASLD PRACTICE GUIDELINES

Hepatology. Feb. 2007

Chronic Hepatitis B

Anna S. F. Lok[1] and Brian J. McMahon[2]

This guideline has been approved by the American Association for the Study of Liver Diseases and represents the position of the Association.

Preamble

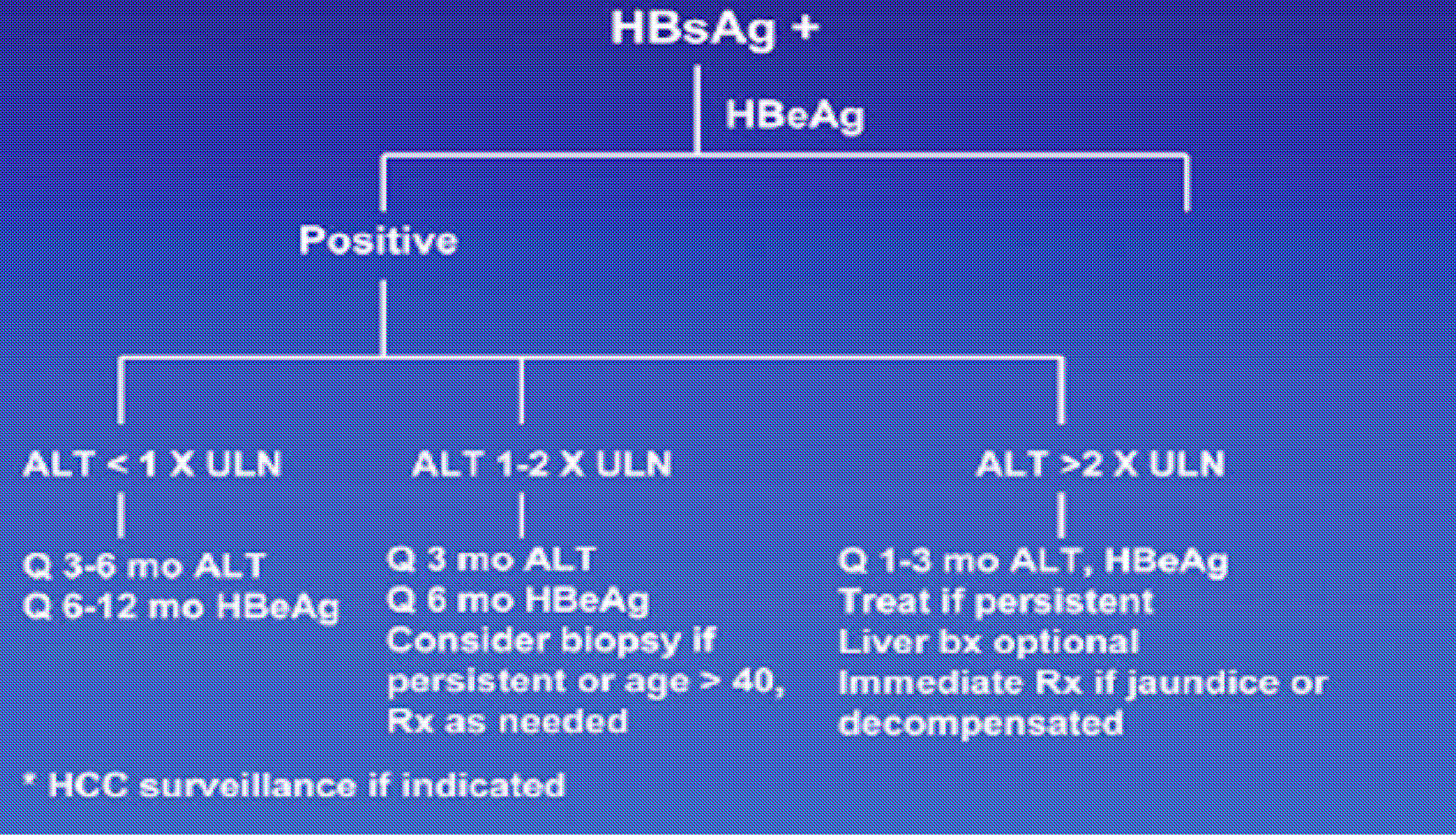
These guidelines have been written to assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected with the hepatitis B virus (HBV). These recommendations provide a data-supported approach to patients with hepatitis B. They are based on the following: (1) formal review and analysis of published literature on the topic — Medline search up to February 2006 and meeting abstracts in 2003-2005; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines [1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines[2]; and (4) the experience of the authors in hepatitis B. In addition, the proceedings of the 2000 and 2006 National Institutes of Health conferences on the "Management of Hepatitis B", the EASL 2002 International dations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible. Specific recommendations are based on relevant published information. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a category to be assigned and reported with each recommendation (Table 1). These guidelines may be updated periodically as new information becomes available.

Introduction

An estimated 350 million persons worldwide are chronically infected with HBV.[7] In the United States, there are an estimated 1.25 million hepatitis B carriers, defined as persons positive for hepatitis B surface antigen (HBsAg) for more than 6 months.[8,9] Carriers of HBV are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[10] Although most carriers will not develop hepatic complications from chronic hepatitis B, 15% to 40% will develop serious sequelae during their lifetime.[11] The following guidelines are an update to previous AASLD

A

Management of Chronic HBV Infection*



* HCC surveillance if indicated

B

Management of Chronic HBV Infection*

HBsAg +

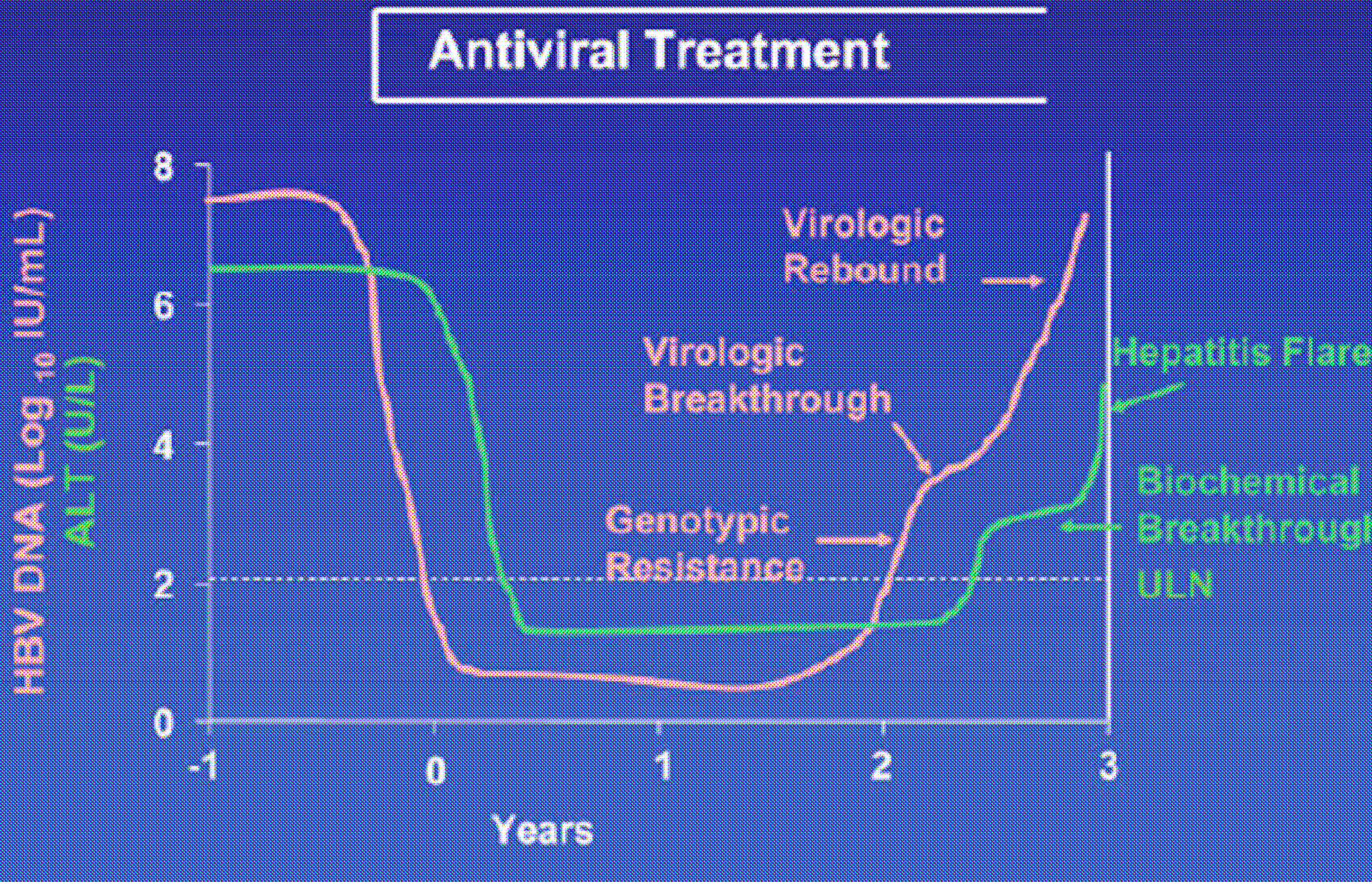
HBeAg

Negative

ALT ≥ 2X ULN	ALT 1-2X ULN	ALT < 1X ULN
HBV DNA ≥ 20,000 IU/mL	HBV DNA 2,000-20,000 IU/mL	HBV DNA < 2,000 IU/mL
Treat if persistent, Liver biopsy optional	Q 3 mo ALT & HBV DNA Consider biopsy if persistent Rx as needed	Q 3 mo ALT X 3, Then Q 6-12 mo If ALT still <1x ULN

* HCC surveillance if indicated

Manifestations of Antiviral Resistance



HBV Infection- treatment…

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Hepatitis B Virus Infection

Jules L. Dienstag, M.D.

REPORTS OF SUCCESSFUL ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B virus (HBV) infection appeared three decades ago,[1] and during the past decade, progress has accelerated dramatically. Along with progress, however, has come complexity. So much more is known now than at the dawn of the antiviral era about the protean clinical expressions of HBV infection that determining whom, when, and how to treat has become progressively more challenging.

VIROLOGIC AND EPIDEMIOLOGIC FACTORS AND NATURAL HISTORY

Dienstag, J. NEJM 359: p.1486ff. 10.2.08

Dienstag, J. NEJM 359: p.1486ff. 10.2.08

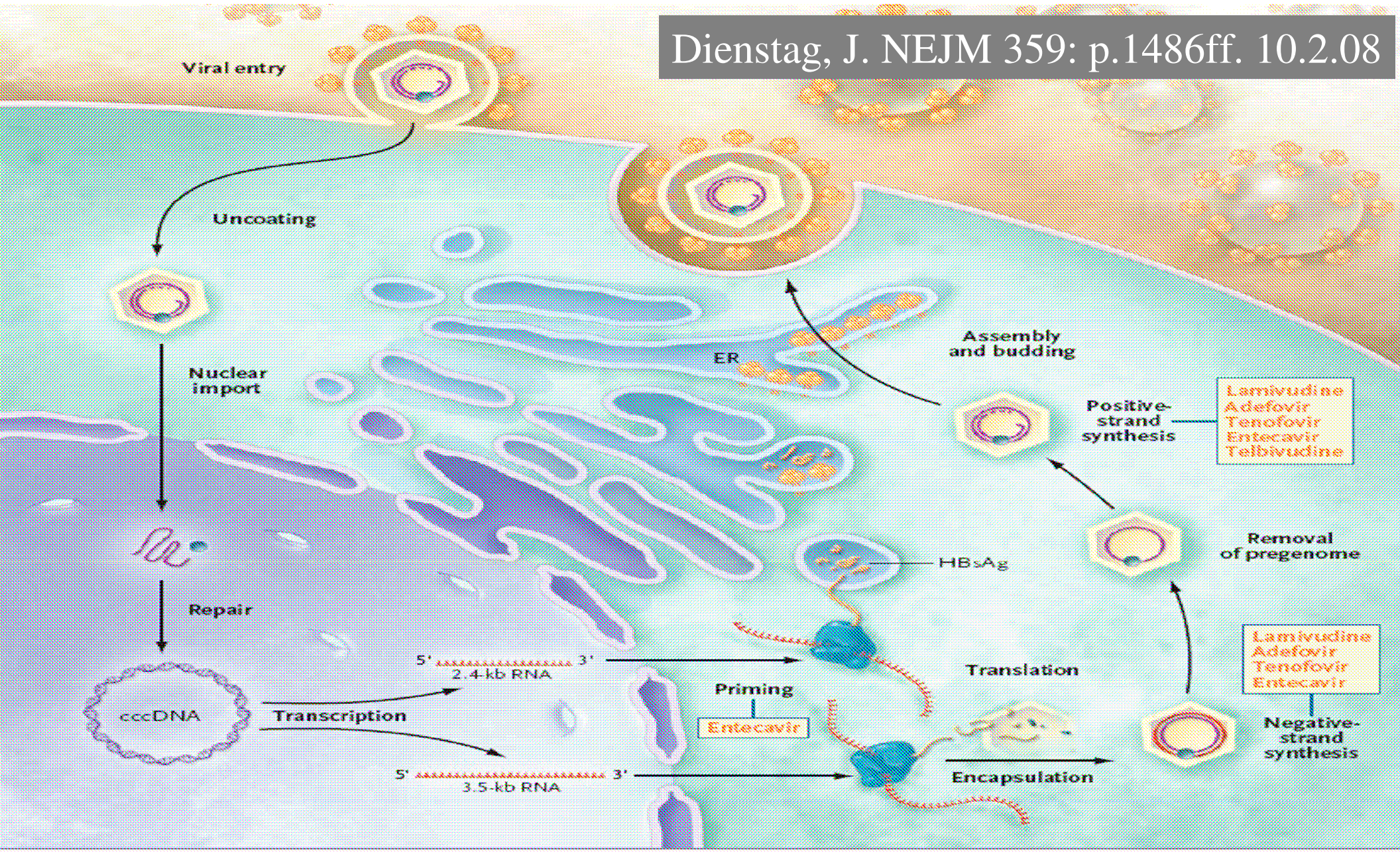


Figure 1. Steps of HBV Replication.

The hepatitis B virus (HBV) establishes covalently closed circular DNA (cccDNA) as a durable miniature chromosome in the host nucleus and relies on a retroviral strategy of reverse transcription from RNA to negative-strand DNA. The steps of HBV replication targeted by nucleoside and nucleotide analogues that are used to treat chronic HBV infection are shown. ER denotes endoplasmic reticulum, and HBsAg hepatitis B surface antigen.

Table 1. Currently Used or Approved Antiviral Therapies for HBeAg-Positive Chronic HBV Infection in Patients Who Have Not Received Treatment.*

Variable	Pegylated Interferon Alfa-2a (Pegasys)†	Lamivudine (Epivir)	Adefovir (Hepsera)	Entecavir (Baraclude)	Telbivudine (Tyzeka)	Tenofovir (Viread)
Route of administration	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Dose	180 μg/wk	100 mg/day‡	10 mg/day‡	0.5 mg/day‡	600 mg/day‡	300 mg/day‡
Duration of therapy — wk§	48	48 to ≥52	≥48	≥48	≥52	≥48
Tolerability	Influenza-like symptoms (e.g., fatigue, fever, and myalgias), cytopenias, depression, anxiety, irritability, autoimmune disorders	Well tolerated	Well tolerated, but creatinine monitoring advisable	Well tolerated	Well tolerated	Well tolerated, but creatinine monitoring advisable
HBeAg seroconversion — %¶						
At 1 yr	27 (32 at 72 wk)	16–21	12	21	22	21
At >1 Yr	NA	Up to 50 at 5 yr	43 at 3 yr	39 at 3 yr	30 at 2 yr	ND
Serum HBV DNA — mean or median reduction in $\log_{10}$ copies/ml at 1 yr	4.5	5.5	3.5	6.9	6.4	6.2
Serum HBV DNA undetectable by PCR — %‖	25	36–44	13–21	67	60	80
ALT normalization at end of 1 yr — %	39	41–75	48–61	68	60	77
HBsAg loss — %						
At 1 yr	3	≤1	0	2	<1	3
At 2 yr	NA	3	ND	5	ND	5 at wk 64
Histologic improvement — %**	38 at wk 72	49–62	53–68	72	65	74
Viral resistance — %						
At 1 yr	None	15–30	None	None††	6	0
At >1 yr	NA	70 at 5 yr	ND	<1% up to 4 yr	22	ND
Durability of the HBeAg response after 1 yr — %‡‡	82	70–80	91	82	80	ND
Approximate cost for 1 yr of treatment — $§§	18,000	2,500	6,500	8,700	6,000	6,000
Strength or weakness	Finite duration, no resistance, 1-yr serologic advantage, injectable, low tolerability	Oral, well tolerated, moderate potency, high resistance	Oral, well tolerated, modest potency, moderate resistance	Oral, well tolerated, high potency, low resistance	Oral, well tolerated, high potency, high resistance	Oral, well tolerated, high potency, low resistance

Table 2. Currently Used or Approved Antiviral Therapies for HBeAg-Negative Chronic HBV Infection in Patients Who Have Not Received Treatment.*

Dienstag, J. NEJM 359: p.1486ff. 10.2.08

Variable	Pegylated Interferon Alfa-2a (Pegasys)†	Lamivudine (Epivir)	Adefovir (Hepsera)	Entecavir (Baraclude)	Telbivudine (Tyzeka)	Tenofovir (Viread)
Serum HBV DNA — mean or median reduction in $\log_{10}$ copies/ml at 1 yr	4.1	4.2–4.7	3.9	5.0	5.2	4.6
Serum HBV DNA undetectable by PCR — %‡	63	60–73	51–64	90	88	95
ALT normalization at end of 1 yr — %	38	62–79	48–77	78	74	79
HBsAg loss — %						
At 1 yr	4	≤1	0	<1	<1	0
At >1 yr	8 at 3 yr after completion of 1 yr of therapy	ND	5 at 4–5 yr	ND	ND	ND
Histologic improvement — %§	48 at wk 72	61–66	64	70	67	72
Viral resistance — %						
At 1 yr	None	15–30	None	None	4	0
At >1 yr	NA	70 at 5 yr	29 at 5 yr	<1 up to 4 yr	9	ND
Durability of the HBV DNA–ALT response after 1 yr — %¶	18	<10	<10	ND	ND	ND

HCV : "The Silent Epidemic"

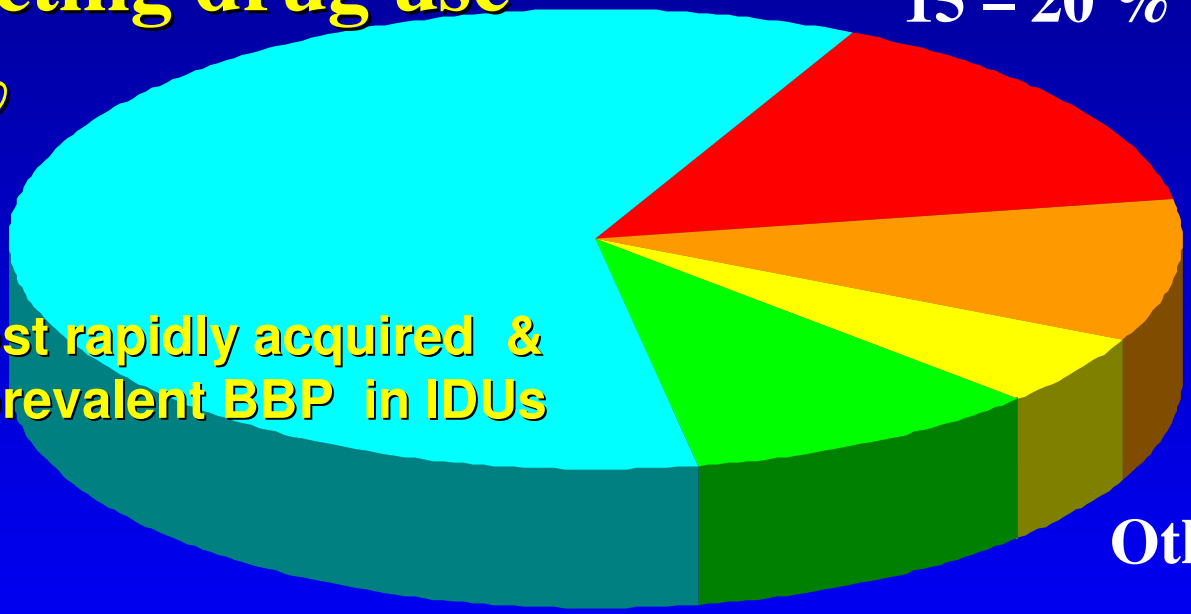
- **THE most common bloodborne pathogen globally & in USA (est. ~4 million persons)**
- **THE leading cause of chronic liver disease in USA (alcohol & HBV/ HCV globally)**
- **THE leading indication for liver transplants in USA**

Sources of Infection for Persons with Acute (Incident) Hepatitis C

Injecting drug use 60%

Sex (multiple partners) 15 – 20 % of cases

prevalence by # s.p.:
50 ~ 9%
10-49 ~ 3%
2-9 ~2%



HCV- the most rapidly acquired & most prevalent BBP in IDUs

Transfusion 10% (before screening in July 1992)

Other* 5%
***Nosocomial**
Health-care work
Perinatal

Unknown 10%

Source: Sentinel Counties, CDC

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

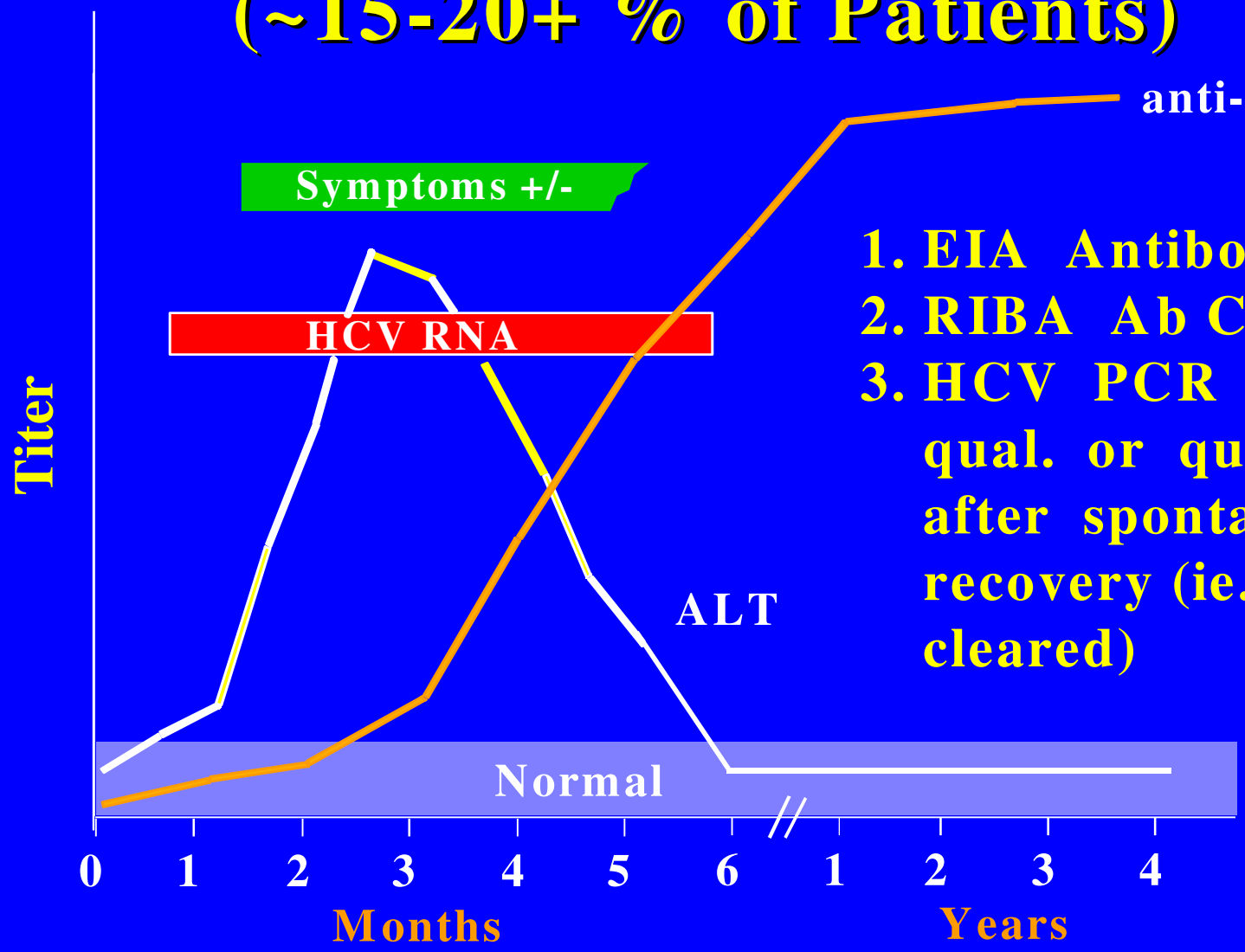
Slide courtesy of CDC/ Division of Viral Hepatitis/ Dr. Miriam Alter

HCV Tests (~ to HIV Tests)

- **HCV EIA** Antibody screen- may be false (+), amount of antibody (signal: cutoff ratio > 3.8) = likely true +
- **HCV RIBA** Ab confirmatory (~ W. Blot for HIV)

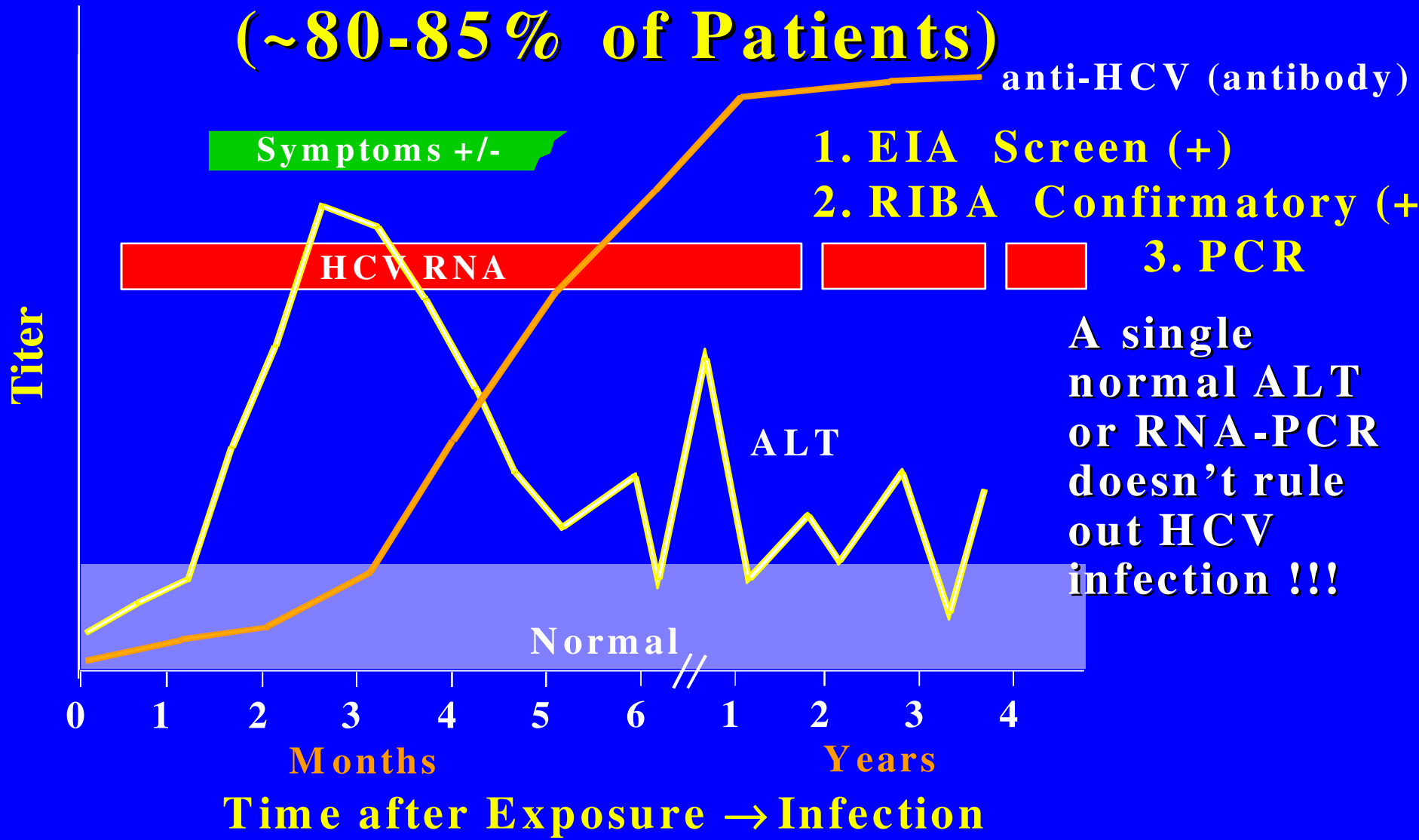
- **HCV bDNA** – measures the virus, not antibody
  - Qualitative (negative or positive) [less expensive]
  - Quantitative (Viral Load, or # of HCV/ ml)
- **HCV PCR RNA** – measures the virus, not antibody (most labs don't perform any more)

Acute HCV Infection with Recovery (~15-20+ % of Patients)



1. EIA Antibody Screen (+
2. RIBA Ab Confirmatory (
3. HCV PCR RNA qual. or quant. is (-) after spontaneous recovery (ie. HCV cleared)

Progression to Chronic HCV Infection (~80-85% of Patients)



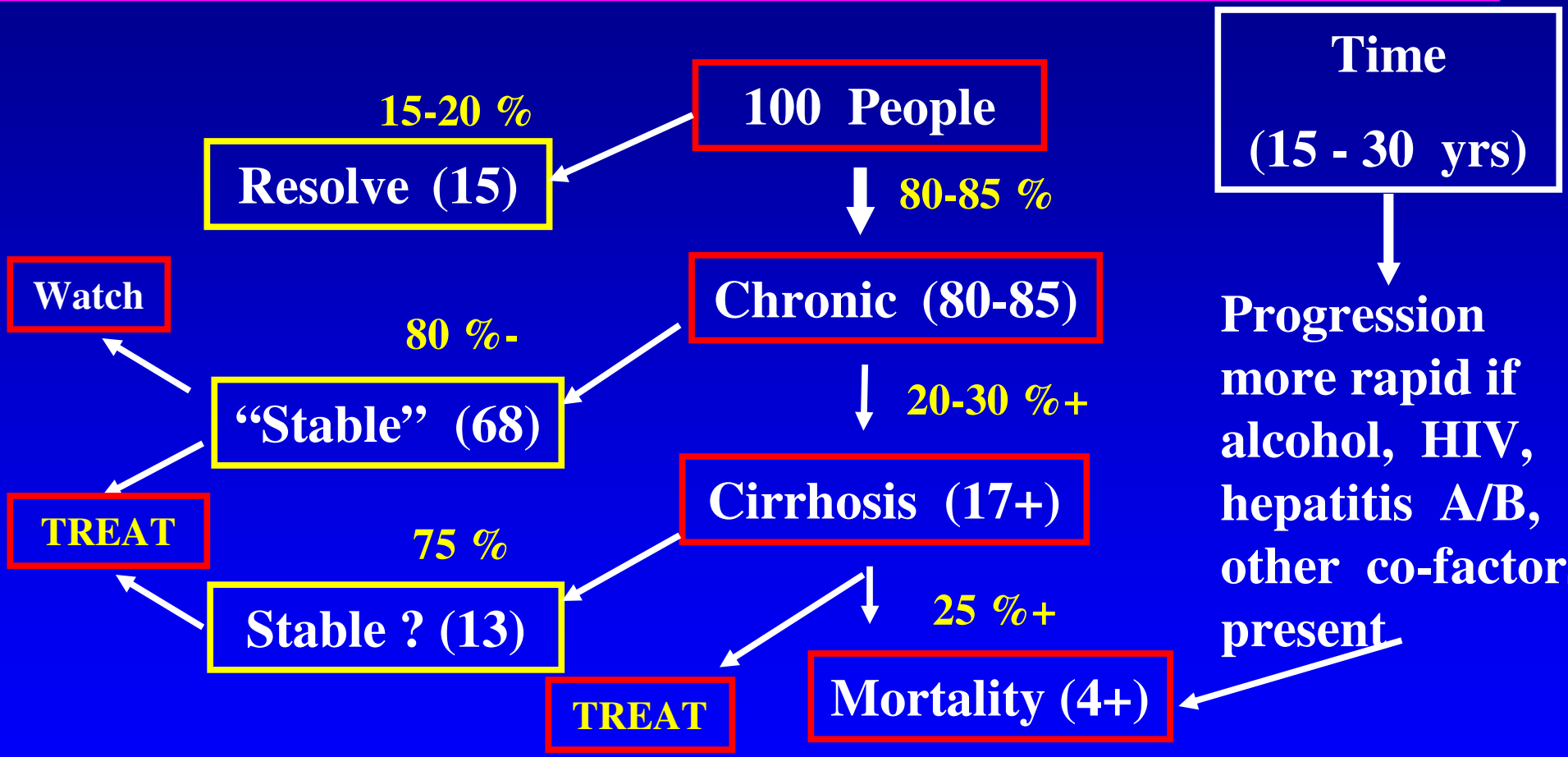
A single normal ALT or RNA-PCR doesn't rule out HCV infection !!!

Hepatitis C Virus (HCV)

Test Interpretation

EIA	RIBA	PCR	Interpretation
Negative			Not infected
Positive	Positive	Positive	Has HCV
Positive	Negative	Negative	False EIA
Positive	Positive	Negative	1. Had HCV, now cleared. 2. A single HCV RNA test result also cannot r/o active infection. Test needs to be repeated.

"Natural History" of HCV Infection *



***Leading Cause of Chronic Liver Dis. & Indication for Liver Transplant**

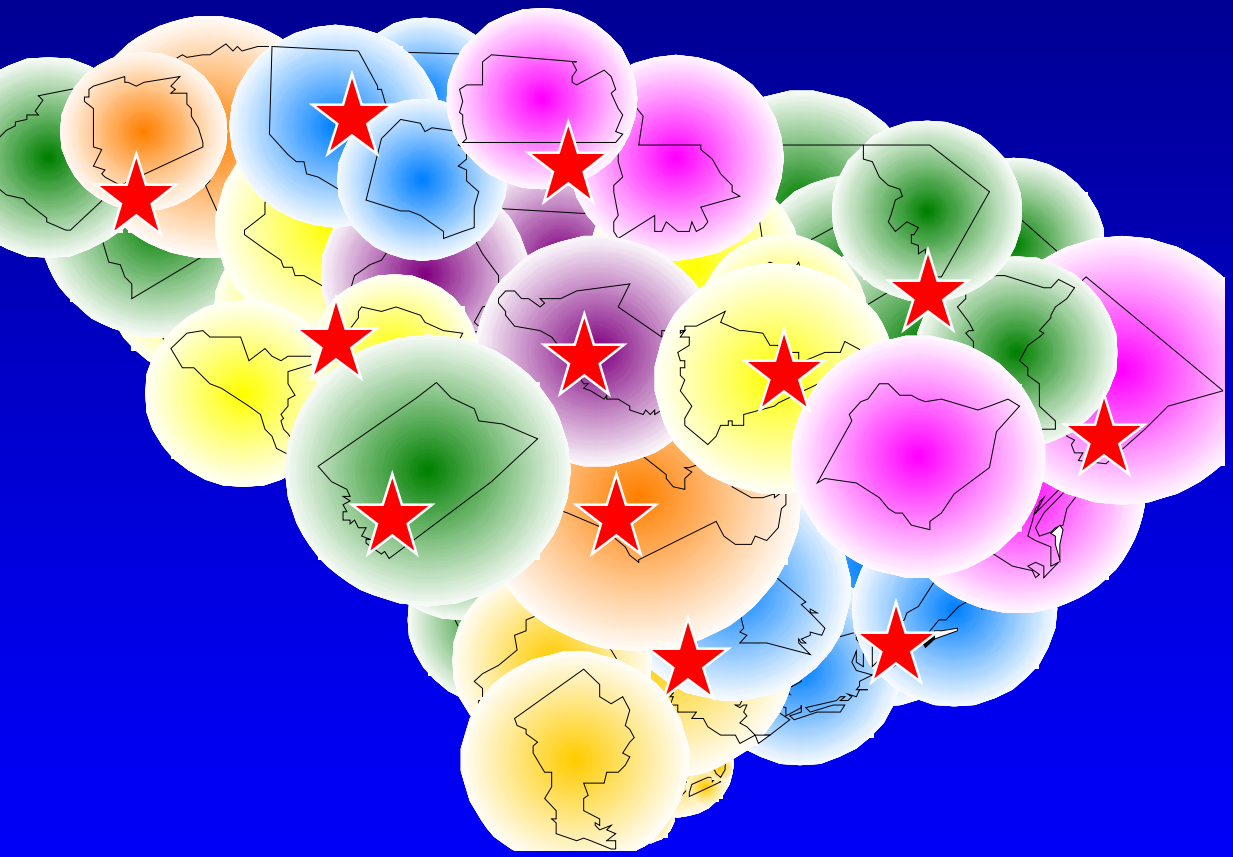
Adapted from Alter HJ

Slide courtesy of Dr. M. Alter/CDC, modified by R Ball (SCDHEC)

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

SCDHEC PROMOTE PROTECT PROSPER

SC DHEC HCV CTRPN Sites 2006



DHEC in 2002→
Hep C Counseling, Testing, Referral, & Partner Notification Services

Essentially free HCV testing for most persons with recognized risk factors (regardless of ability to pay)

If (+), also get PCR and Viral Load, and attempts to refer to PMD for f/up & care

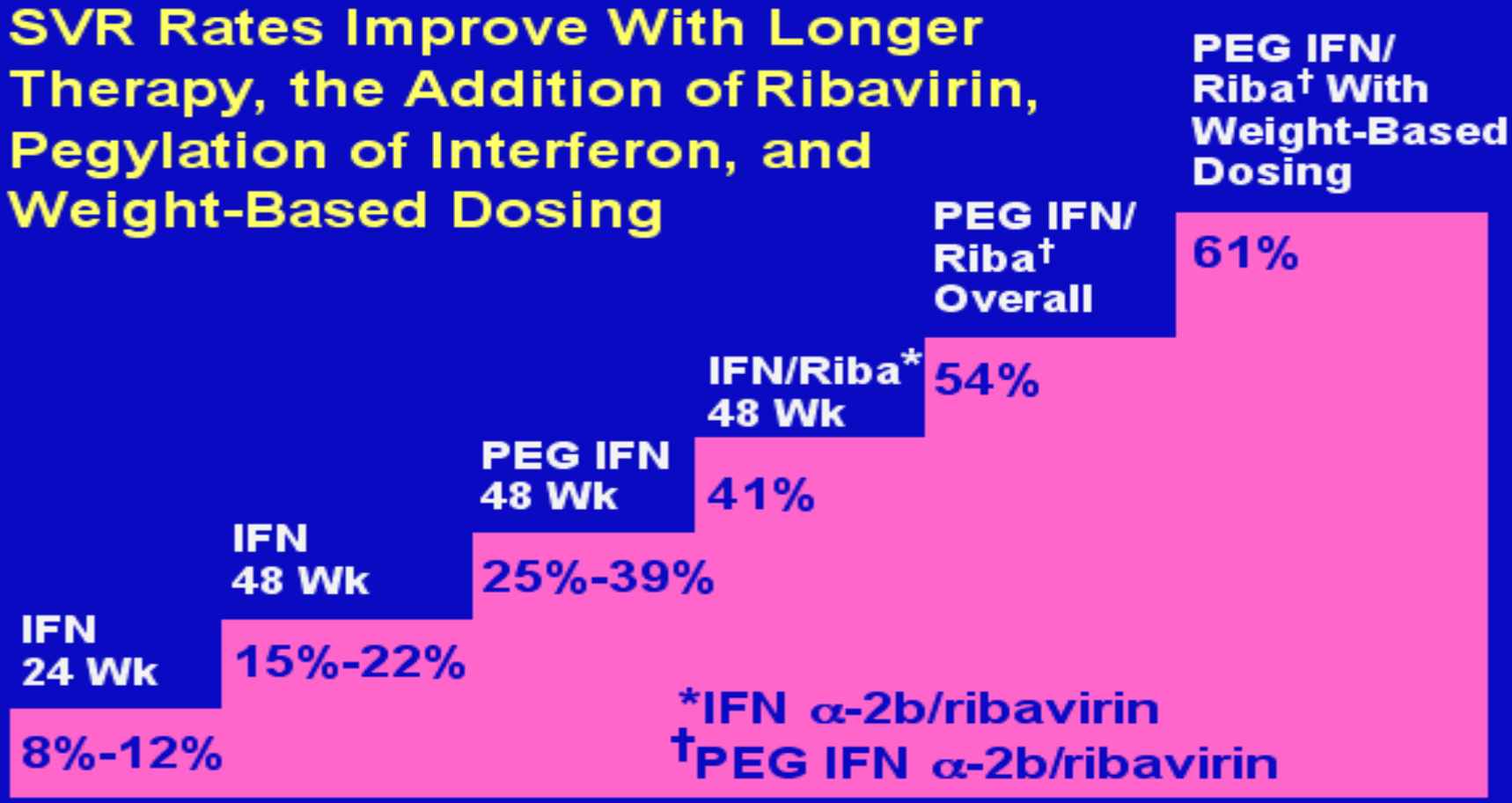
R. Ball, MD, MP

HCV : SC Testing, Referrals, Treatment

- HCV testing for years by private MDs, others
- Individual benefits of knowing one's status:
  - Prevent further liver damage (ie, avoid alcohol)
  - Prevent transmission to others (ie, sex partners)
  - Refer for medical evaluation – status of chronic liver disease, plan followup, evaluate as candidate for curative therapy

- *Current combination medications can CURE approx. 2/5 – 3/5 persons completing therapy*

Improved Cure Rates of HCV - 2001 (~ 3 of 5 persons completing therapy)



D H E C
PROMOTE PROTECT PROSPER

R. Ball, MD, MPH

Tx of Acute HCV Infection in HCWs

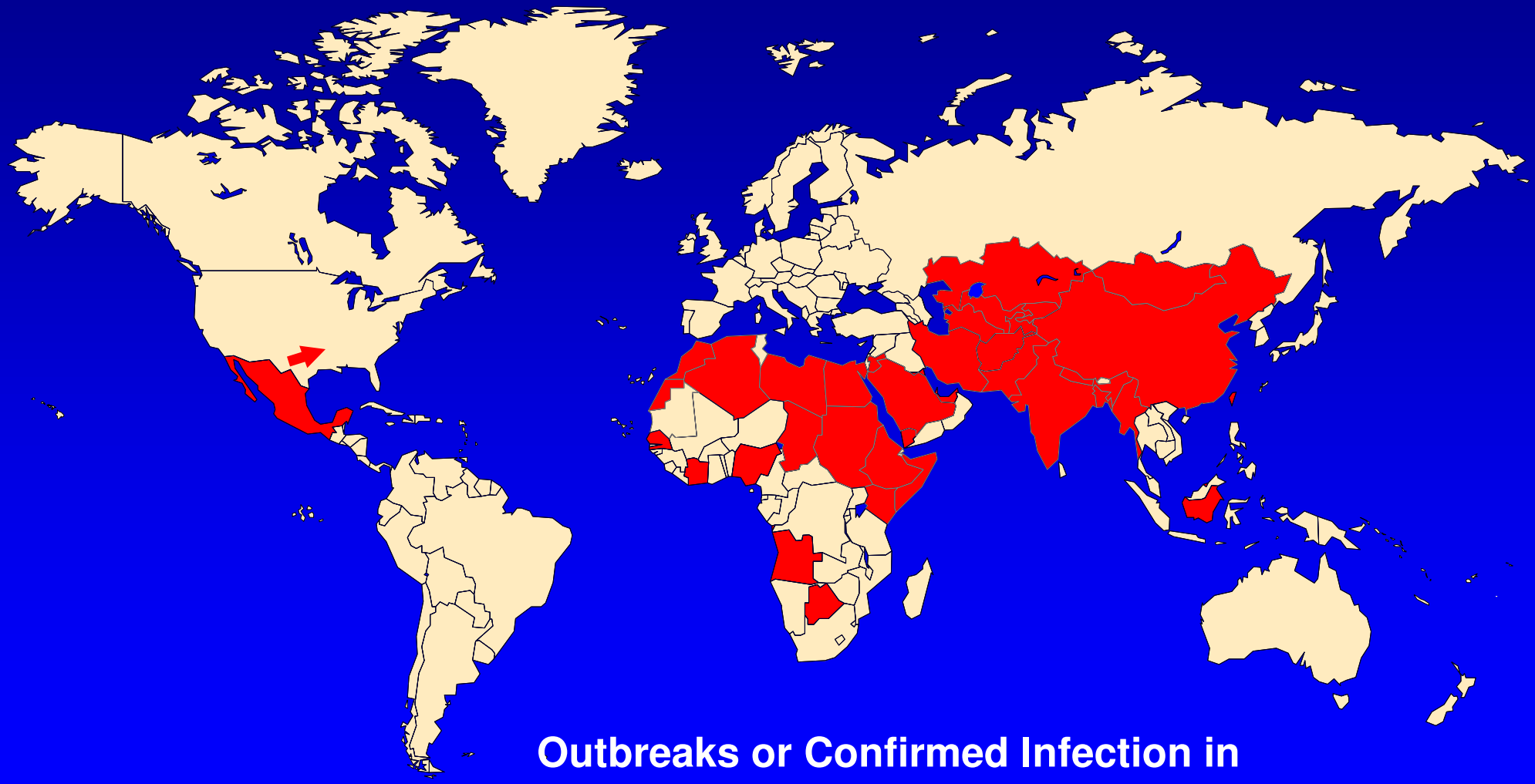
- 44 symptomatic acutely HCV infected (Dx ≤ 4 months)
- HCWs-needlesticks/ sex/ IDU/ surgery; 61% genotype 1
- Mean incub.period ~8wks, ALT~885, viral load ~420 K
- Tx: Interferon 5 mIU qD x 4 wk → 3x/ wk: total 24 wks
- 6 months after Tx: 43/44 HCWs had undetectable HCV
- **~ 98% CURE RATE WITH EARLY MONO-Tx**

- Jaeckel E, et al. Early Treatment of Acute Hepatitis C Infection with Interferon-alfa 2b Monotherapy Prevents Development of Chronic Hepatitis HCV Infection. Abstract # 634. 51st Annual Meeting of the American Association for Study of Liver Diseases (AASLD), October 2000 → **Treatment of Acute Hepatitis C with Interferon alfa-2b NEJM 345 (#20) : 1452-7, 11/15/01 (www.nejm.org 10/01/01)**

Delta Hepatitis (HDV)

- Present ONLY when patient has (+) HBsAg (ie, HBV infection)
- 95% in IDUs w/ HBV
- Almost never tested for, even by specialists
- US prevalence apparently declining (but poor testing rates, reporting/ surveillance)
- Suspect if Pt is IDU, has HIV, HBV & is sicker than expect, other clinical situations…

Geographic Distribution of Hepatitis E



Outbreaks or Confirmed Infection in
> 25% of Sporadic Non-ABC Hepatitis

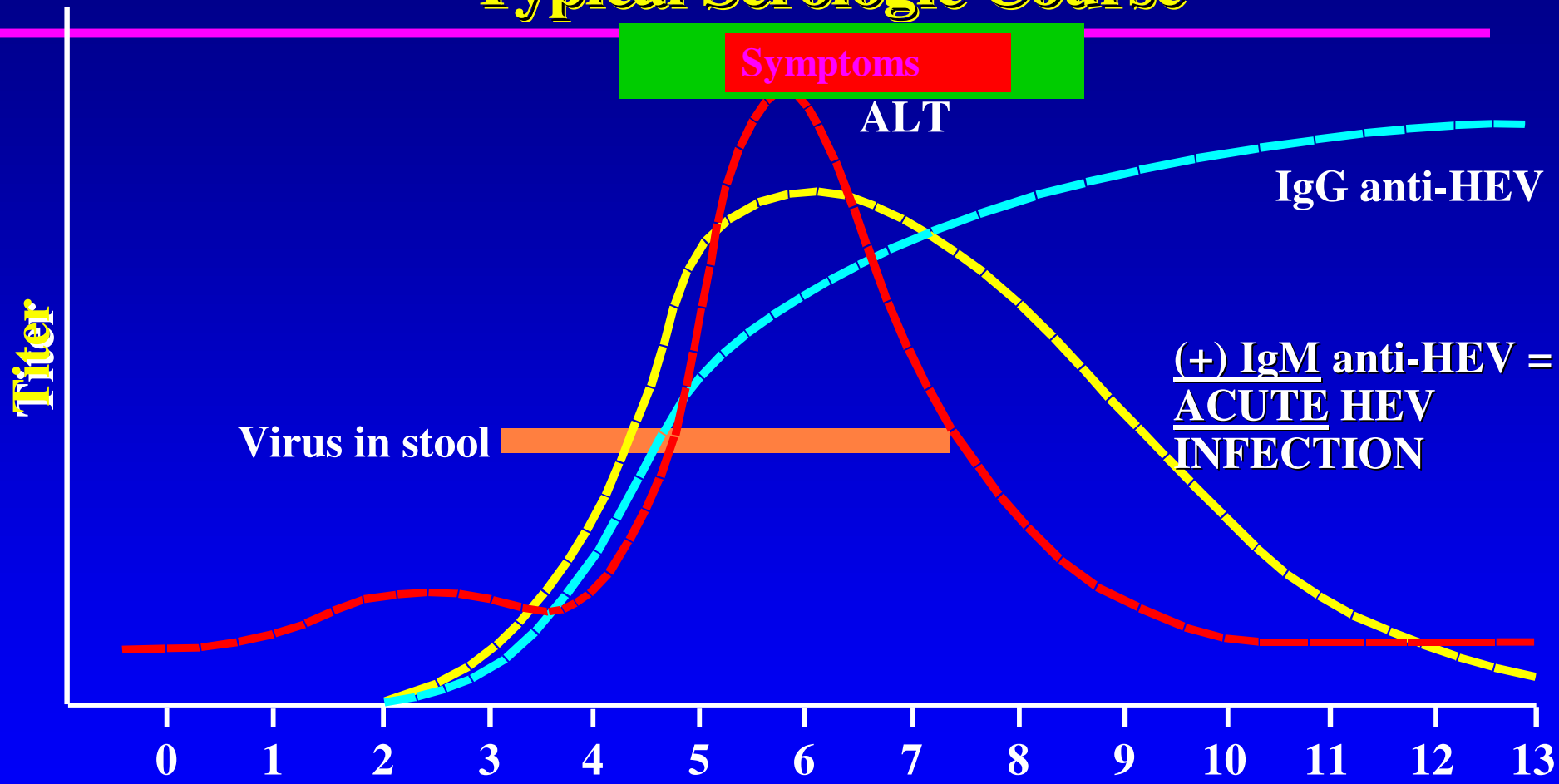
R. Ball, MD, MPH

Hepatitis E – Clinical Features

Incubation period:	Average 40 days Range 15-60 days
Case-fatality rate:	Overall, 1%-3% Pregnant women, 15%-25%
Illness severity:	Increased with age
Chronic sequelae:	None identified

Hepatitis E Virus Infection

Typical Serologic Course



CDC

Hepatitis E: Epi Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas
- IG PEP does not prevent infection
- No specific therapy (usu. self-limited)

What about Human Bite Mx & Hepatitis Transmission ?

Recommendations

2006 Red Book

American Academy of Pediatrics

CDC. MMWR June 29, 2001

Updated US Public Health Service Guidelines...

"Feces, nasal secretions, **saliva**, sputum, sweat, tears, urine, and vomitus are **not** considered potentially infectious unless they contain (visible) blood." – CDC

(however, HBV may be transmitted via saliva in unique cases)

BITE MANAGEMENT ISSUES

- 2 PERSONS INVOLVED: "BITER" (aggressor) & "BITEE" (victim); often complex circumstances
- EVALUATE: if biter's **saliva** → bitee's wound ?
- HIV & HCV are NOT transmitted via saliva "unless contain (visible) blood" (prior to bite); HBV can be…
- EVALUATE: if bitee's **blood** → biter's mouth (risk of bitee BBP transmission to biter's mucous membrane)
- Consult (public health) re: testing both people for BBPs
- Consider other (more likely) pathogens (ie, bacteria)

Raison d'etre

"Act, before disease becomes persistent through long delays."

- Ovid (43 BC – 17 AD)

(as quoted by Laurie Garrett, in her book
Betrayal of Trust: The Collapse of Global Public Health)

The mind can absorb only as much as the fanny can endure. Thank you for your interest. Questions?

"Those who carry on great public schemes must be proof against the most fatiguing delays, the most mortifying disappointments, the most shocking insults, and what is worst of all, the presumptuous judgments of the ignorant."

- Edmund Burke (1729 - 1797)